ISSN: 1608-9677

JEMDSA

Journal of Endocrinology, Metabolism and Diabetes of South Africa

JEMDSA 2017 Volume 22 Number 1 (Supplement 1) Page S1-S196 www.jemdsa.co.za

The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes

SEMDSA Type 2 Diabetes Guidelines Expert Committee.

JEMDSA 2017; 22(1)(Supplement 1): S1-S196

SEMDSA
Society for Endocrinology, Metabolism and Diabetes of South Africa

GUIDELINE CONTENTS

JEMDSA
Journal of Endocrinology, Metabolism and Diabetes of South Africa

SEMDSA 2017 Guidelines for the Management of Type 2 diabetes mellitus

JEMDSA
Journal of Endocrinology, Metabolism and Diabetes of Southern Africa

SEMDSA Guidelines
52nd SEMDSA Congress and 15th LASSA Congress
5-7 May 2017

2017 SEMDSA Guideline Committees

Chair / Editor-In-Chief

Aslam Amod

Editorial and Review Committee

Aslam Amod
Ankia Coetzee
Tanya E. Kinvig
Imran Paruk
Zaheer Bayat
Joel A. Dave
Nazeer A. Mohamed
Fraser J. Pirie

Expert Committee

Razana Allie
RN (ICU)
Chairperson: DESSA
Diabetes Nurse Educator
Johannesburg

Aslam Amod
MBChB, FCP(SA), Cert Endo & Metab; FRCP(London)
Department of Diabetes and Endocrinology (part-time)
Nelson R Mandela School of Clinical Medicine
University of KwaZulu - Natal

Zaheer Bayat
MBBCh, FCP(SA), Cert Endo & Metab
Division of Endocrinology
Helen Joseph Hospital
University of the Witwatersrand

Dirk J. Blom
MBChB (UCT), MMed (UCT), FCP (SA), PhD
Associate Professor & Head of Division
of Lipidology
University of Cape Town

Susan L. Brown
MBChB, FCP(SA), Cert Endo & Metab
Endocrinologist
Head of Department, Mahatma Gandhi
Memorial Hospital, Durban

Michelle Carrihill
MBChB; DCH; FCPaeds; Cert Endo & Metab (Paeds); MPhil (Paed Endo)
Paediatric Endocrinology, Department of Paediatrics
University of Cape Town

Ria Catsicas
BSC Dietetics (NWU), BA Psychology (UNISA), MSc Nutrition (US)
Registered Dietitian, Nutritional Solutions
Johannesburg

Ankia Coetzee
MBChB; MMed, FCP(SA), Cert Endo & Metab.
Division of Endocrinology
Tygerberg Academic Hospital and Stellenbosch University.

Joel A. Dave
MBChB(UCT), PhD(UCT), FCP(SA), Cert Endo & Metab.
Associate Professor
Division of Diabetic Medicine and Endocrinology
University of Cape Town and Groote Schuur Hospital

Larry A. Distiller
FCP(SA), FRCP, FACE
Hon. Lecturer, University of South Wales
Centre for Diabetes and Endocrinology
Houghton, Johannesburg

Nasrin Goolam Mahyoodeen
FCP(SA), Cert. Endo. & Metab. (SA)
Division of Endocrinology
Chris Hani Baragwanath Academic Hospital
University of the Witwatersrand

Tanya E. Kinvig
BSC, MBChB(UCT), FCP(SA), Cert Endo & Metab.
Vincent Pallotti Hospital
Cape Town

Paul Rheeder
MMed(IntMed) FCP(SA) PhD
Professor, Department of Internal Medicine
Steve Biko Academic Hospital,
University of Pretoria.

Hamish J van Wyk
MSc Diabetes, Diploma in Diabetes, BSc Dietetics
Hon. Lecturer, University of South Wales
Centre for Diabetes and Endocrinology
Johannesburg

Lourentia van Wyk
B.Sc (Dietetics); Registered Diabetes Educator
Department of Human Nutrition
Tygerberg Academic hospital and
Stellenbosch University

The Advisory Committee

Societies

SEMDSA (ACE-SA and LASSA)
Department of Health
Diabetes South Africa
Faculty of Consulting Physicians of South Africa
South African Medical Association
Diabetes Education Society of South Africa (DESSA)
IPA Foundation of South Africa
Society for General/Family Practitioners
Council of Medical Schemes
Medical Schemes Administrators

Members

Simon Ackerman
Laura Blacking
Margaret Campbell
Debbie Gordon
Mahomed A Khalek
Thabiso Mofokeng
Louisa Roux
William Toet
Leegale Adonis
Freek Bester
Philip Erasmus
Sedeshan Govender
Adri Kok
Kershlin Naidu
Sundeep Ruder
Jeffrey Wing
Zeenat Barday
Francois Bonnici
Henrieke Fagan
Kate Kgasi
Tasneem Mahomedy
Ian Ross
Itumeleng Setlhare

External Reviewers

Dr. Tony Behrman
Family Practitioner
Cape Town

Dr. Angelique Coetzee
Family Practitioner
Pretoria

Dr. Parimala Govender
Family Practitioner
Umkomaas

Dr. Stan Landau
Specialist Physician
Johannesburg

Dr. Elijah Nkosi
Family Practitioner
Soweto

Dr. Rajen S Pillay
Family Practitioner
Durban

Dr. Freek J Bester
Specialist Physician
Bloemfontein

Dr. Richard Darby
Family Practitioner
Kwa Zulu-Natal

Dr. Uttam Govind
Family Practitioner
Durban

Dr. SP Moodley
Obstetrician
Durban

Dr. Trevenasen Padayachee
Family Practitioner
Umkomaas

Prof. Brian Rayner
Division of Hypertension and
Nephrology
University of Cape Town and Groote
Schuur Hospital

Dr. Marius Wasserfall
Specialist Physician
Cape Town

Prof Morgan N. Chetty
IPA Foundation

Dr. Govindsamy (Jeff) Govender
Family Practitioner
Port Elizabeth

Dr. Adri Kok
Specialist Physician
Johannesburg

Dr. Sagie Naidu
Obstetrician
Durban

Dr. Rajen Pather
Obstetrician
Durban

Prof. P Soma-Pillay
Professor and Head: Obstetrics
Steve Biko Academic Hospital &
University of Pretoria

Disclaimer

These guidelines are not intended to replace professional judgment, experience and appropriate referral. These guidelines are intended to inform general patterns of care, to enhance diabetes prevention efforts and to reduce the burden of diabetes complications in people living with this disease. They reflect the best available evidence at the time, and practitioners are encouraged to keep updated with the latest information in this rapidly changing field. While every care has been taken to ensure accuracy, reference to product information is recommended before prescribing. SEMDSA assumes no responsibility for personal or other injury, loss or damage that may result from the information in this publication.

Unless otherwise specified, these guidelines pertain to the care of adults with type 2 diabetes at primary healthcare level.

Website

An electronic version of these guidelines is available at www.semdsa.org.za. Any corrections after the printing of this edition and before the next will be available on this website. Comments about the guidelines can also be sent via the website.

Reproduction of the Guidelines

Citation

To cite these guidelines as a whole:

The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.

To cite a specific chapter:

The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. “Chapter Title” in 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.

Introduction

The Guideline development process

The process we followed in developing the guideline was as follows:

1. The SEMDSA Executive Committee (SEMDSA Excom) tasked the 2012 guideline committee chairperson to co-ordinate an update of type 2 diabetes guideline at the end of 2015.
2. The steering committee from the previous guideline was contacted to volunteer to continue the guideline development and update in their particular fields of expertise. This group became the SEMDSA 2017 Type 2 Guidelines Expert Committee (Expert Committee).
3. The guideline process was guided by the AGREE II recommendations for guideline development.[1]
4. The need for the guideline update was identified and communicated to the Expert Committee. These were:
    a. The lack of a suitably applicable international guideline for South African circumstances.
    b. To incorporate new updated information in multiple sections
    c. To simplify and rewrite some "difficult to read" sections
    d. To increase the use of summarised recommendations
    e. To correct errors and improve referencing
    f. To attempt to incorporate "levels of evidence" and "strength of recommendations" into the guideline
5. The objectives of the guideline were defined for The Expert Committee:
    f. The population targeted for benefit from this guideline was to be individuals with type 2 diabetes, and those at high risk for developing type 2 diabetes, who access care at a primary healthcare facility.
    g. To provide guidance on the most appropriate management for people with diabetes mellitus and its complications at primary health care level.
    h. To enhance diabetes prevention efforts with the goal of reducing the burden of diabetes and its complications at primary healthcare level.
    i. To inform clinical decisions in type 2 diabetes made by primary healthcare professionals and funders
6. For this purpose we identified 29 areas of focus (the chapters), and each expert was allocated to oversee guideline development in one or more areas. The Experts were free to co-opt others to assist in the process.
7. Each expert was tasked with asking and answering key questions relevant to the objectives, within their areas of expertise. They were advised to conduct rigorous literature searches and reviews, but this was not methodically defined.
8. A Guideline Strategy and Planning Meeting was held in Johannesburg on 27/28 February 2016. In addition to the Expert Committee, the following participants and stakeholders were invited to this meeting (The Advisory Committee):
    a. All members of the Association of Clinical Endocrinologists of South Africa (ACE-SA, a subgroup of SEMDSA)
    b. Diabetes Education Society of South Africa (DESSA) – four delegates
    c. Representatives from the South African Department of Health (Non-Communicable Diseases Directorate) – four delegates
    d. Representatives from the Council of Medical Schemes - two delegates
    e. Representatives from Faculty of Consulting Physicians of South Africa – two delegates
    f. South African Medical Association – two delegates
    g. Board of Healthcare Funders - two delegates
    h. IPA Foundation of South Africa - two delegates
    i. The South African Heart Association - two delegates
    j. Medical Scheme Administrators – Discovery, Momentum, Medscheme, GEMS, MHG – one delegate each
    k. No pharmaceutical or other industry representation or sponsorship was allowed at any stage.
9. At the Guideline Meeting, members of the Expert Committee were required to present and discuss the proposed changes to their allocated chapter. The proposals were interrogated and debated by those present, and amendments and additions were suggested. The discussions were evidence based, and where evidence was lacking, a consensus among participants was adopted.
10. Following the Guideline Meeting, the Expert Committee members conducted a further review of any controversial issues, and amended the chapters to reflect the discussions and consensus from the meeting.
11. The chapters were then circulated for external review and revised when necessary.
12. The Editorial and Review Committee then reviewed each chapter:
    a. For errors, omissions and duplication.
    b. To create uniformity of layout and style.
    c. To review, amend or generate tables and appendices where appropriate.
    d. To review, amend or formulate recommendations based on the chapter content.
    e. To grade the strength of the recommendations based on SORT taxanomy (Figure 1).[2]

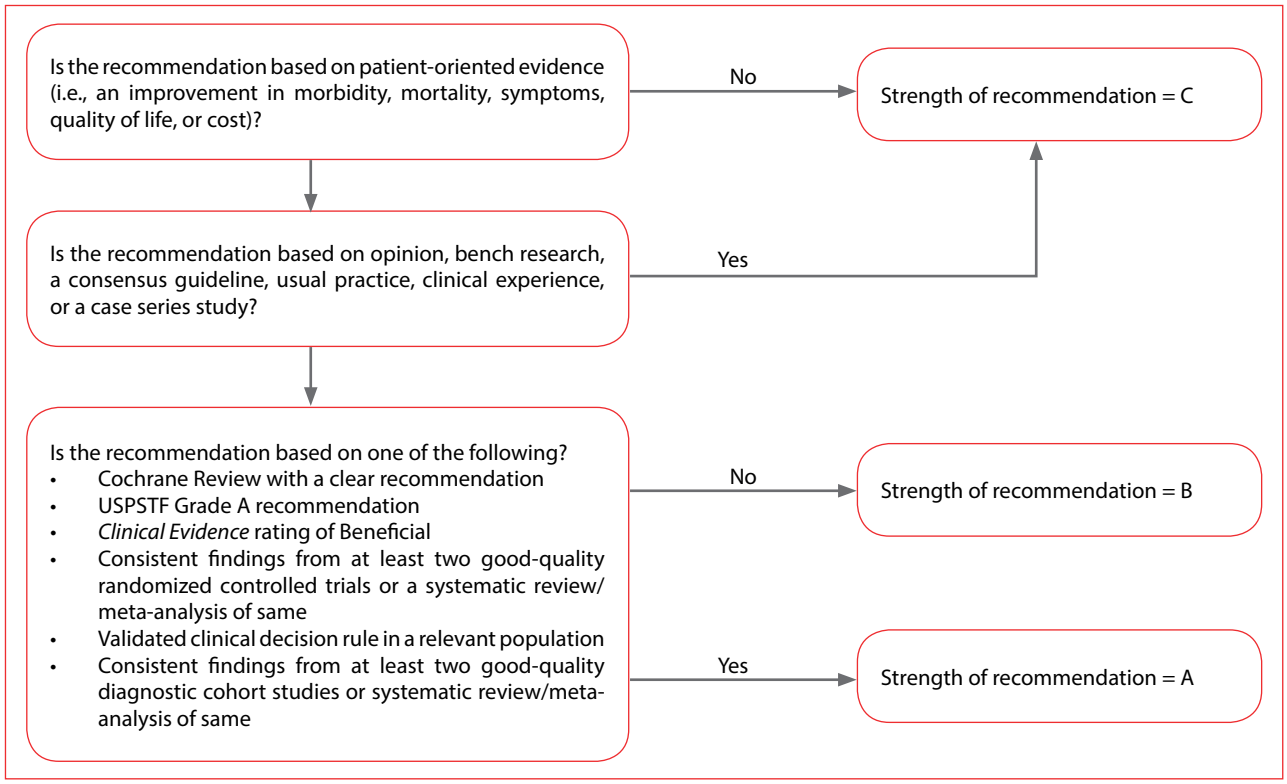


Figure 1: The Strength Of Recommendations Taxonomy (SORT) for grading of evidence.[2]
USPSTF = U.S. Preventive Services Task Force

13. The reviewed and edited chapters were circulated to members of the Expert Committee for final approval and then submitted for publication.
14. The Expert Committee was guided primarily by best-evidence and best-practice considerations, taking into account the general, and dichotomous, socio-economic environment in South Africa. Consequently, our recommendations apply to all people living with type 2 diabetes in South Africa.
15. This entire guideline development process including its publication was funded independently by SEMDSA.
16. All authors and editors have disclosed their dualities to the Chairperson.
17. All Committee members performed their tasks voluntarily and received no remuneration for their services.

Next update

SEMDSA will assess the need for an update in 2020 or sooner if circumstances dictate this.

Acknowledgements

The Chairperson and SEMDSA wish to record our sincere appreciation to:

- The Expert Committee for their dedication and efforts in producing these guidelines.
- The members of the Editorial and Review Committee who, apart from their tasks as contributors to various chapters, also sacrificed an enormous amount of personal time in reviewing and editing the final document.
- All of the External Reviewers for giving up their time and expertise to assist with this task.
- Healthman (SEMDSA secretariat) and especially Joey Hanekom for her administrative and logistical assistance in coordinating the guideline meetings.
- Dr. Sundeep Ruder for keeping records of the guideline meeting.
- Medpharm Publications, including Prof Oppel BW Greef, Robyn Marais, Chantelle Janse van Rensburg, Ina du Toit, and other publishing staff for their professional assistance, and extreme patience and understanding in publishing the guideline.
- The Canadian Diabetes Association for allowing SEMDSA permission to use and adapt sections of the Canadian Diabetes Association Clinical Practice Guidelines (2008).

Aslam Amod

Chairperson

References

1. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: Advancing guideline development, reporting and evaluation in health care. J Clin Epidemiol. 2010;63(12):1308-1311. doi:10.1016/j.jclinepi.2010.07.001.
2. Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): A Patient-Centered Approach to Grading Evidence in the Medical Literature. J Am Board Fam Med. 2004;17(1):59-67. doi:10.3122/jabfm.17.1.59.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 1: Epidemiology of type 2 diabetes

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations
The estimated national prevalence of diabetes (based on HbA_{1c}) in persons older than 15 years was 9.5% (2012), and about 45% of these individuals were undiagnosed. An additional 9% of the South African population had abnormal glucose regulation defined by an HbA_{1c} between 6.0 and 6.4%.
The Asian and Coloured populations have the highest prevalence of diabetes in South Africa.
The prevalence of diabetes in rural dwellers appears to be increasing rapidly.
The number of people living with diabetes in Africa is predicted to increase by 140% by the year 2040.
The number of deaths globally from diabetes exceeded the combined mortality from HIV/AIDS, tuberculosis and malaria in 2015.
There are clearly modifiable risk factors driving the diabetes epidemic; the rising prevalence of obesity is one of the most important.

1.1. Background and Introduction[1, 2]

1.1.1. Sub-Saharan Africa (SSA)

Diabetes mellitus (diabetes) affects people worldwide and poses major public health and socio-economic challenges. The disorder was previously thought to be rare or undocumented in rural Africa, but over the past few decades it has emerged as an important non-communicable disease (NCD) in sub-Saharan Africa (SSA). After the introduction of standardised diagnostic criteria, King and Rewers showed in 1993, that diabetes in adults was a global disorder and that populations of developing countries, minority groups and disadvantaged communities in industrialised nations faced the greatest risk. Subsequently, several reports on global estimates and projections confirmed the diabetes epidemic and indicated that the numbers of people with diabetes and prevalence of both diabetes and impaired glucose tolerance (IGT) will rise. The increases are expected to be largest in developing regions of the world because of population ageing and urbanisation.[1]

Estimates from 2015 by the International Diabetes Federation (IDF) (Table 1) suggest that the number of adults with diabetes in the world will increase by 55% in 2040. The greatest increase is anticipated for the Africa region, with a 140.9% projected increase. IGT in SSA is expected to rise in the same period, by 126.4%; this will likely contribute to the higher burden of future diabetes. Therefore, the proportionate increase for SSA is more than double the predicted global increase for both IGT (51.3%) and diabetes (54.7%).[2]

The regional prevalence of diabetes for the Africa region for 2015 was 3.2% (2.1-6.7%) and expected to increase to 3.7% (2.6-7.3%) by 2040. This region has the highest proportion (66.7%) of undiagnosed diabetes. The majority (58.8%) of people with diabetes live in cities, although the population in the region is predominantly (61.3%) rural; as urbanisation increases and populations age, type 2 diabetes will pose an increasing threat. Nearly half of all adults with diabetes in the region live in the four most populous countries: South Africa (2.3 [1.2-4.6] million), Democratic Republic of Congo (1.8 [1.5-2.2] million), Nigeria (1.6 [1.2-3.8] million) and Ethiopia (1.3 [0.8-3.5] million).[2]

In 2015, there were 321 100 deaths attributable to diabetes for the Africa region, with more than 79% occurring in the economically productive age group i.e. age < 60 years, the highest proportion of any region and 1.7 times higher in women than in men. Globally approximately 5.0 million people aged between 20 and 79 years died from diabetes in 2015, equivalent to one death every six seconds. This is higher than the combined number of deaths from HIV/AIDS (1.5 million), tuberculosis (1.5 million), and malaria (0.6 million) in 2013. Close to half

Table I: IDF Estimates for 2015 and 2040[2]

Number of adults (20-79 years) with diabetes:			
	Number (million) [uncertainty range]		**Projected increase**
	2015	2040	
World	415 [340-536]	642 [521-829]	+55%
Africa	14.2 [9.5-29.4]	34.2 [23.7-67.7]	+140.9%
Number of adults (20-79 years) with IGT			
SSA	34.9 [21.0 - 96.8]	[48.3-222.3]	+126.4%

(46.6%) of deaths due to diabetes are in people under the age of 60.[2]

In 2015, the estimated health expenditure on diabetes in Africa was USD 3.4 billion, accounting for 0.5% of the global expenditure, the lowest for any region; this is equivalent to 7.0% of the region's total health budget and to USD 24.3 - 419 person / year.

In addition to the present challenges of resource depletion, countries in SSA face the double burden of communicable diseases (e.g. HIV/AIDS, tuberculosis) and non-communicable diseases (NCD) and their risk factors (e.g. diabetes).

The IDF report also highlighted the paucity of data sources for the Africa region with a total of 13 sources from 12 countries selected. More than three quarters of countries lacked nation-wide data; only a few SSA countries (Kenya and South Africa) had data sources based on oral glucose tolerance test (OGTT); diabetes prevalence figures for other countries in the region were based on studies that used self-reports, fasting blood glucose, were older than five (5) years and may be underestimates. The report highlighted the urgent need for further epidemiological research and improved data collection systems in the region.

1.1.2. South Africa

South Africa is ranked as an upper middle-income economy by the World Bank and the United Nations (UN). It has one the largest economies in Africa. It is a country of contrasts, with wide divides between the "haves" (privileged) and the "have-nots" (underprivileged), where at least a quarter of the population is unemployed and lives on USD 1.25 per day. It is a country where traditional values grapple with the onslaught / entrenchment of the technological age and which has undergone rapid socio-political changes over the past two decades.

From the most recent (2011) population census, the total population is 51.770,560 million, living in nine (9) provinces with 11 official languages; >60.0% live in urban areas. Africans (Blacks) constitute 79.2% (41 million) of the total population; South Africa has the largest European, Asian Indian and Mixed Ancestry communities in Africa.

Against this background, this section provides an overview of the burden (epidemiology) of type 2 diabetes in non-pregnant adults in South Africa.

1.2. Epidemiology of diabetes mellitus in South Africa

1.2.1. IDF estimates

Based on the most recent 2015 IDF estimates for South Africa, there were 2.286 (1.1637-4.6206) million adults (20-79 years) with diabetes; the national prevalence was 7.0% (3.6-14.1) with a comparative prevalence of 7.6% (3.1-14.7). Of the 2.3 million people with diabetes, 1.3968 (0.603-2.3944) million (61.1%) were undiagnosed. The mean health expenditure per person with diabetes was USD 918.9 USD (1736.1 international dollars); and there were 57,319 diabetes related deaths.[2]

The following will provide a brief overview of the epidemiology studies undertaken from the 1960's to the present.

1.2.2. Local studies[1,3–5]

a. Early studies (prior to standardised criteria)

Before the introduction of standardised WHO criteria for glucose tolerance and since the early 1960's, several studies examined the prevalence of diabetes in South Africa. However, such studies involve different study populations, methodologies and criteria for the diagnosis of diabetes. Despite these limitations, such studies showed prevalence rates ranging between 0.6 - 3.6% in urban communities.[1, 3-5]

b. Studies using standardised WHO/ADA criteria

Appendix 1 summarises the studies on diabetes prevalence undertaken from the 1980's.[1,3–6] Since the introduction of standardised WHO criteria and methodology for the diagnoses of diabetes in 1985, there have been several studies undertaken in South Africa in urban, peri-urban and rural communities; the majority of the published studies have used the 1985 WHO criteria. In these studies, from three provinces (KwaZulu Natal, Western Cape and Free State), the age standardised prevalence was 4.8% in peri-urban and 5.3-8.0% in urban Africans (Blacks), 10.8% in Mixed ancestry (Coloured) communities, and 13.0% in Asian Indians. All the studies reported age-standardised prevalence rates.

Using current (1998 WHO) criteria, moderate prevalence (3.9%) has been reported in rural KwaZulu Natal and high rates in urban Africans in Cape Town (13.1%) and Durban (12.9%) and in Mixed ancestry populations in the Western Cape (26.3%) (Appendix 1).[1,3–6]

c. Longitudinal studies

To date, the only longitudinal studies which have examined the incidence of diabetes or the natural history of intermediate stages of glucose intolerance (IFG, IGT) in South Africa, have been in Asian Indians in Durban. There was a high risk of progression to diabetes in Indians with IGT (50.4% over four (4) years; rate of progression: 12.6% per annum). In a 10-year follow-up study, the age and sex adjusted cumulative incidence of diabetes was 8.3% (rate of progression 0.95% per annum; incidence density 8.3/1000 person years). [1,3–5]

d. South African National Health and Nutrition Examination Survey (SANHANES) 2012 (Appendix 2)

The Human Science Research Council embarked on the SANHANES to recruit and establish a nationally representative cohort of 5 000 South African households to be followed up over the coming years. The first cross-sectional examination (SANHANES-1) was completed in 2012 and reported in 2014.[7]

The final population sample included 25 532 people from 6 305 households who were interviewed, and then subsequently invited to a clinic examination and blood biomarker analyses for lipid profiling and HbA_1c. The results for the prevalence of HbA_1c and other metabolic abnormalities are summarised in Appendix 2.

The national prevalence of abnormal glucose regulation (as defined by the cut-points used) was 18.6%. The prevalence figures are more startling when the analysis is confined to individuals older than 45 years where 16-25% of the population had diabetes and an additional 11-20% had sub-diabetic but abnormal HbA_{1c}. It is noteworthy that HbA_{1c} in the range 6.1 to 6.4% is not equivalent to IFG or IGT; it is known to underestimate intermediate hyperglycaemia (IFG and IGT). Nevertheless it is well established as a risk factor for progression to diabetes.[8–10] In SANHANES-1 only 5% of individuals knew that they had diabetes implying that 45% of diabetes was previously undiagnosed. It is also worrying that no sector of society appeared to be protected; the highest prevalence of diabetes was found in rural informal dwellers (11.9%) and urban formal dwellers (11.3%). The prevalence of diabetes was equal among Blacks and Whites (just over 8%), higher among Coloureds (13.4%) and peaked at 30% for Asians.

1.2.2.1. Africans (Blacks)

a. Prevalence

Both from earlier and recent studies, whatever criteria are used and when compared with other studies using oral glucose tolerance test (OGTT), both rural and urban prevalence in South Africa are higher than in other parts of SSA and comparable with that found in developed countries. [1–5]

Regarding intermediate hyperglycaemia, IGT rates are moderate (4.8%) in rural communities but high in urban Xhosa in whom the prevalence of IGT has increased by 67%, from 7.0% in the 1990's to 11.7% in 2009. IFG prevalence was low both in rural (1.5%) and urban (1.2%) studies. A high prevalence of total disorders of glycaemia has been reported in both urban and rural communities. The foregoing also underscores the need for OGTT in epidemiology studies in SSA to identify those with IGT when estimating future trends in diabetes; IGT and IFG are not interchangeable and denote different abnormalities of glucose regulation.

More importantly, there is now clear evidence of an increase in the prevalence over the past few decades. Studies from the urban Cape Town study showed that when 1995 WHO criteria are applied, there has been a 52.5% increase, from 8.0% in the 1990's to 12.2% in the recent study in 2009, both in men and women, and across age groups. imilar findings are shown in the recent study in Durban (5.3% in 1984 vs. 12.9 % in 2014).

b. Risk factors for diabetes

South Africa as for the rest of SSA, is at grave risk for an increase in NCD especially diabetes, because of the many different and interrelated risk factors both modifiable and non-modifiable. These include the high proportions of undiagnosed diabetes in rural South Africans, the urban-rural differences and impact of urbanisation, ageing and peak prevalence in the older age group, the association with positive family history, adiposity, diminished physical activity and psycho social factors, as well as the impact of HIV/AIDS. In addition the global prevalence of obesity, a major risk factor for diabetes, is rising rapidly and in SSA, rates of obesity are among the fastest growing in the world.[2,11] Since 1980, WHO estimates that the worldwide prevalence of obesity has more than doubled, with significant increases seen in every region. In sub-Saharan Africa, the number of overweight children grew from 4 million in 1990 to 10 million in 2012.[12]

Summary

The data on the epidemiology of type 2 diabetes in South Africa has confirmed moderate to high diabetes prevalence and higher than in other SSA countries using the same methodology and comparable with those in developed countries; it explodes the previously held myth that diabetes is rare on this continent and there is now confirmatory evidence that the prevalence has increased over the past few decades. Diabetes prevalence is higher in urban and migrant populations and they are clearly identifiable and modifiable risk factors for its development.

Author: Ayesha A. Motala
Editor: Aslam Amod

References

1. Mbanya JCN, Motala AA, Sobngwi E, Assah FK, Enoru ST. Diabetes in sub-Saharan Africa. Lancet. 2010;375(9733):2254-2266. doi:10.1016/S0140-6736(10)60550-8.
2. International Diabetes Federation. IDF Diabetes Atlas, 7 ed. Int Diabetes Fed. 2015. http://www.idf.org/diabetesatlas. Accessed January 2, 2016.
3. Peer N, Kengne A-P, Motala AA, Mbanya JC. Diabetes in the Africa region: An update. Diabetes Res Clin Pract. 2014;103(2):197-205. doi:10.1016/j.diabres.2013.11.006.
4. Motala AA, Omar MAK, Pirie FJ. Epidemiology of Type 1 and Type 2 Diabetes in Africa. Eur J Cardiovasc Prev Rehabil. 2003;10(2):77-83. doi:10.1177/174182670301000202.
5. Levitt NS. Diabetes in Africa: epidemiology, management and healthcare challenges. Heart. 2008;94(11):1376-1382. doi:10.1136/hrt.2008.147306.
6. Hird TR, Pirie FJ, Esterhuizen TM, et al. Burden of Diabetes and First Evidence for the Utility of HbA1c for Diagnosis and Detection of Diabetes in Urban Black South Africans: The Durban Diabetes Study. Staiger H, ed. PLoS One. 2016;11(8):e0161966. doi:10.1371/journal.pone.0161966.
7. Shisana O, Labadarios D, Rehle T, et al. South African National Health and Nutrition Examination Survey, 2012 (SANHANES-1). In: 2014th ed. Cape Town: HSRC Press; 2014:1-397.
8. Nathan DM, Balkau B, Bonora E, et al. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. Diabetes Care. 2009;32(7):1327-1334. doi:10.2337/dc09-9033.
9. Bonora E, Tuomilehto J. The Pros and Cons of Diagnosing Diabetes With A1C. Diabetes Care. 2011;34(Supplement_2):S184-S190. doi:10.2337/dc11-s216.
10. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379(9833):2279-2290. doi:10.1016/S0140-6736(12)60283-9.
11. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet. 2016;387(10026):1377-1396. doi:10.1016/S0140-6736(16)30054-X.
12. World Health Organization. Obesity and diabetes: the slow-motion disaster. Keynote address at the 47th meeting of the National Academy of Medicine. WHO. 2016. http://www.who.int/dg/speeches/2016/obesity-diabetes-disaster/en/. Accessed April 2, 2017.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 2: Definition and classification of diabetes mellitus

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Recognise that the clinical stages of hyperglycaemia include intermediate hyperglycaemia (impaired fasting glucose and impaired glucose tolerance) and diabetes mellitus. Intermediate hyperglycaemia represents a high-risk state for future diabetes and cardiovascular disease.	C
Always consider the aetiological classification of diabetes mellitus at diagnosis and review this periodically. Be aware that latent auto-immune diabetes of adulthood, maturity onset diabetes of the young, other endocrinopathies, glucocorticoid-induced diabetes and pancreatic diabetes are not uncommon disorders.	C
The clinical distinction between type 1 and type 2 diabetes can be difficult especially in younger individuals, and in those with ketosis-prone (type 2) diabetes. These individuals should be referred to an endocrinologist without delaying treatment.	C
The need for insulin treatment at diagnosis cannot be used as the basis for aetiological classification.	C
Be aware that the classification of hyperglycaemia first detected in pregnancy has been updated by the World Health Organisation and adopted by SEMDSA (refer to Chapter 22).	C

Since 1965, there have been several guidelines for the classification and diagnosis of diabetes mellitus. The first standardised guidelines were published 30 years ago. It was recognised that, as more information relevant to the diagnosis became available, there would be a need to review the classification and diagnostic criteria. There are no major changes to the definition of diabetes mellitus. The classification of hyperglycaemia in pregnancy has been updated, and the importance of making a correct aetiological diagnosis of diabetes is highlighted.

2.1 Definition of diabetes mellitus

Diabetes mellitus (diabetes) is a metabolic disorder with heterogeneous aetiologies, which is characterised by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. The long-term relatively specific effects of diabetes include development of retinopathy, nephropathy and neuropathy. People with diabetes are also at increased risk of other diseases, including cardiac, peripheral arterial and cerebrovascular disease.[1-4]

Diabetes may present with characteristic symptoms such as thirst, polyuria, polydipsia, blurred vision, weight loss and sometimes polyphagia. The most severe clinical manifestation is ketoacidosis or non-ketotic hyperosmolar state, which may lead to stupor, coma, and, in the absence of treatment, death. However, often, symptoms are not severe or may be absent, and consequently in the absence of routine biochemical screening, hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made. There is a major need for improved screening for diabetes, particularly as a significant percentage of cases (30–80%) remain undiagnosed.[1,4,5]

Several pathogenic processes are involved in the development of diabetes. These include processes that impair or destroy the function of the pancreatic beta cells, with consequent *insulin deficiency*, and others that result in resistance to insulin action *(insulin resistance versus insulin insensitivity)*. Abnormalities of carbohydrate, fat and protein metabolism are due to the deficient action of insulin on target tissues, resulting from insensitivity to or lack of insulin, or both.[1-4]

2.2 Classification of diabetes and other categories of glucose tolerance[1-6]

The classification encompasses both the *clinical stages* and *aetiological types* of diabetes, and other categories of hyperglycaemia (Figure I and Table I).[1,3,5,6] References 1 and 3 can be consulted for more details.

2.2.1 Clinical Stages of glucose tolerance

Regarding the *clinical stages*, the spectrum of glucose tolerance extends from normoglycaemia, to intermediate hyperglycaemia [impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to diabetes, regardless of underlying aetiology.

IFG and IGT are high-risk states for diabetes or categories of increased risk for diabetes. The 2011 World Health Organisation (WHO) Consultation[4] affirmed the position taken by the 2006 WHO/IDF (International Diabetes Federation) consultation[5], that no further change should be made to the 1999 WHO recommendations[1] on the diagnostic criteria for these states, discourages the use of the term "pre-diabetes" to describe IGT and IFG because of its misleading implication that all such individuals will inevitably progress to diabetes, and endorses the continued use of the collective term "intermediate hyperglycaemia". IFG and IGT should not be viewed as clinical entities in their own right,

Table I: Aetiological classification of diabetes mellitus[1,3,5,6]

I. Type 1 diabetes (β cell destruction, usually leading to absolute insulin deficiency)
A. Immune mediated
B. Idiopathic
II. Type 2 diabetes
May range from predominantly insulin resistance with relative insulin deficiency, to a predominantly secretory defect with insulin resistance. Also includes a subset who have ketosis-prone diabetes.
III. Other specific types
A. Genetic defects of β cell function
Maturity onset diabetes of the young (MODY) – currently 11subtypes, neonatal diabetes mellitus, mitochondrial DNAs
B. Genetic defects in insulin action
Type A insulin resistance, Donahue syndrome (Leprechaunism), Rabson-Mendenhall syndrome, lipoatrophic diabetes, others
C. Diseases of the exocrine pancreas
Pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy, others
D. Endocrinopathies
Acromegaly, Cushing's syndrome, glucagonoma, phaeochromocytoma, hyperthyroidism, others
E. Drug or chemical induced
Glucocorticoids, nicotinic acid, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, interferon, pentamidine, diazoxide, atypical antipsychotics, highly active antiretroviral therapy (HAART)
F. Infections
Congenital rubella, cytomegalovirus, others
G. Uncommon forms of immune-mediated diabetes
"Stiff-man" syndrome, anti-insulin receptor antibodies, others
H. Other genetic syndromes sometimes associated with diabetes
Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreich ataxia, Huntington chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome, others
IV. Hyperglycaemia first detected in pregnancy
A. Gestational diabetes
B. Diabetes mellitus in pregnancy

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, allow for aetiological classification.

but rather as risk factors for diabetes and cardiovascular disease (CVD). IFG and IGT are associated with obesity (especially central or visceral), dyslipidaemia with high triglycerides and/or low HDL cholesterol, and hypertension, a constellation collectively referred to as the metabolic syndrome.[2-3] This is discussed in further detail in Chapter 16.

It is important to note that it may only be possible to establish the aetiology of diabetes retrospectively. Diabetes, regardless of the aetiology, progresses through several clinical stages during its natural history, and an individual may progress from stage to stage in either direction. Persons who have, or who are developing, diabetes can be categorised by clinical stage according to clinical characteristics, even in the absence of information on the underlying aetiology (Figure I). Classification is important for determining therapy, but some individuals cannot be clearly classified as type 1 or type 2 diabetes at the time of diagnosis.[1-3, 5,6] Any difficulty in accurate classification should not delay initiation of therapy in symptomatic patients.

2.2.2 Aetiological classification of diabetes mellitus

The *aetiological types* of diabetes are type 1, type 2, other specific types and gestational diabetes (Table I). Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, allow for an aetiological classification.

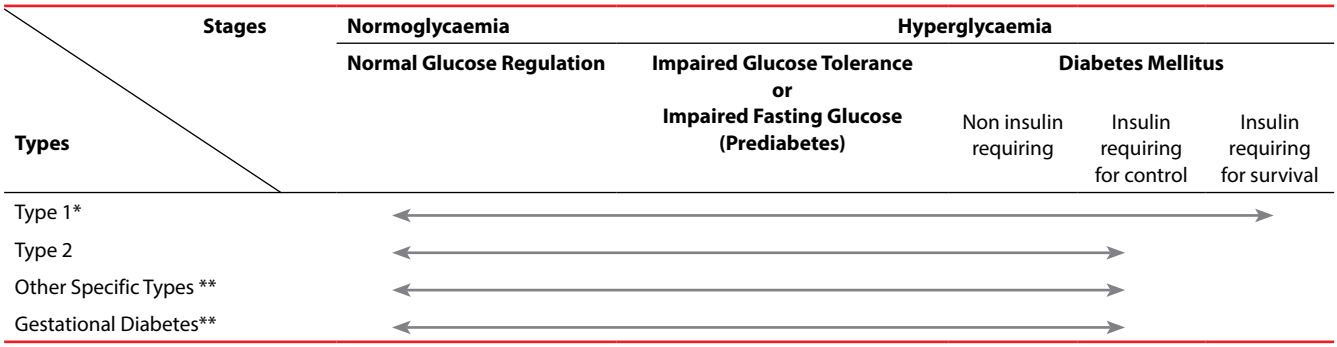
Type 1 diabetes, which accounts for only 5-10% of cases, results from pancreatic beta-cell destruction leading to absolute insulin deficiency. These patients are prone to ketoacidosis, coma and death. Type 1 diabetes may be immune-mediated or idiopathic (no known aetiology). Latent autoimmune diabetes in adults (LADA) is also classified as type 1diabetes.

Type 2 diabetes is the most common aetiological type (90-95% of cases) and is due to a progressive loss of insulin secretion on the background of insulin resistance (disorder of insulin action); it ranges from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance.

Other specific types of diabetes include a wide variety of conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drugs. Some of these are not uncommon and practitioners should be aware of these.

The clinical distinction between type 1, type 2 and other specific types of diabetes can sometimes be difficult, particularly in adolescents and young adults. Type 1 and more especially type 2 diabetes are essentially clinical diagnoses of exclusion i.e. they require the practitioner to at least consider and reasonably exclude other causes of diabetes mellitus. It is estimated that about 15% of patients in general practice are misdiagnosed or misclassified[7] and this can have important therapeutic and prognostic implications.

Figure I: Disorders of glycaemia: aetiological types and clinical stages[1,3,5,6]



*Even after presenting in ketoacidosis, these patients can briefly return to normoglycaemia without requiring continuous therapy (i.e., "honeymoon" remission).
**In rare instances, patients in these categories (e.g. type 1 diabetes presenting initially in pregnancy, post-pancreatectomy) may require insulin for survival.

Table II: Clinical differences between type 1 diabetes and type 2 diabetes

Type 1 diabetes	Type 2 diabetes
Usually younger (<30 years*) but not always.	Usually older but prevalence in children, adolescents and young adults increasing
Usually lean weight	Mostly overweight or obese
Onset is acute	Onset is insidious / gradual
Almost always symptomatic (polyuria, polydipsia, weight loss)	Often asymptomatic
Prone to ketosis, often ketoacidotic at diagnosis	Not usually ketosis prone but ketoacidosis may be present at diagnosis
Diagnosis – usually has unequivocal hyperglycaemia	Diagnosis often during routine screening
Insulin necessary from diagnosis for survival	Usually controlled with non-insulin therapies, or may need insulin for symptom control
Otherwise normally healthy	Often have comorbidities (hypertension, dyslipidaemia, sleep apnoea, fatty liver disease, polycystic ovary syndrome); often diagnosed after emergency admission for myocardial infarction or stroke

*<35 years in African populations

Table II highlights the clinical differences that may assist in making the distinction between type 1 and type 2 diabetes in childhood, adolescents and young adults. Type 2 diabetes includes a subset of adults who have *ketosis-prone diabetes*. Although diabetic ketoacidosis occurs more commonly in patients with type 1 diabetes, it is becoming increasingly evident that there is a sub-set of patients with type 2 diabetes that present with or develop ketoacidosis, yet, after a few months, can be weaned off treatment with insulin and maintain euglycaemia only with oral agents. Most of these patients have a family history of type 2 diabetes and have the typical phenotype of type 2 diabetes, namely acanthosis nigricans and increased waist circumference.[8]

Maturity onset diabetes of the young (MODY) represents a group of autosomal dominant single gene disorders resulting in impaired insulin secretion, with the onset of diabetes in adolescence or early adulthood.[9] These patients typically have no or mild symptoms, lack the typical phenotype of the obese insulin-resistant type 2 diabetes patient, and have a strong family history of early onset (typically before age 25) diabetes in preceding generations. MODY is estimated to account for 1-2% of diabetes cases and is often misdiagnosed as type 1 or type 2 diabetes. The differences in treatment and prognosis, as well as the need for genetic counselling behoves the clinician to have a strong index of suspicion for MODY in patients presenting with "type 2 diabetes" before age 25.

Latent autoimmune diabetes of adulthood (LADA) is a form of type 1 diabetes often misdiagnosed as type 2 diabetes.[10] It is characterised by a slower autoimmune destruction of beta cells than is seen in typical type 1 diabetes, and hence a slower more smouldering onset of hyperglycaemia, not unlike type 2 diabetes. Phenotypically, patients with LADA are older than the typical type 1 diabetes patient (older than 25 years but more usually older than 35 years), are more likely to be non-obese and lack the strong family history of diabetes that is so typical of type 2 diabetes. However these features are not invariable. Approximately 10% of patients over the age of 35 labelled as having type 2 diabetes, may actually have LADA.[10,11] Patients with LADA should be treated with insulin.

Hyperglycaemia in the range characteristic of diabetes, IFG or IGT is also a common feature of *other endocrinopathies* such as thyrotoxicosis, hypothyroidism, Cushing's syndrome and acromegaly. The clinician should always have a high index of suspicion for these secondary causes of hyperglycaemia and investigate or refer when clinically appropriate. Although the concurrent hyperglycaemia may necessitate treatment in its own right, patients with these conditions should be re-evaluated for diabetes if and when the underlying disorder has been treated.

Any doubt about the aetiological classification of diabetes should trigger referral to an endocrinologist for clinical and laboratory evaluation without unnecessarily delaying treatment of the hyperglycaemia.

Gestational diabetes (GDM), was until recently referred to as hyperglycaemia (glucose intolerance) with onset or first recognition during pregnancy. The terminology and classification has been updated since the 2012 SEMDSA guideline. The ADA defines GDM as diabetes diagnosed in the second or third trimester of pregnancy that is not clearly either type 1 or type 2 diabetes.[2, 3] The recent report of the WHO recommends that hyperglycaemia first detected at *any time* during pregnancy should be classified as either 'diabetes mellitus in pregnancy" if the diagnostic criteria for diabetes in non-pregnant adults are met, or "gestational diabetes" for lesser degrees of hyperglycaemia defined by fasting, 1-hour and 2-hour post-glucose load values.[8] SEMDSA endorses and adopts the WHO recommendations.[12] This is discussed further in Chapter 22: Diabetes in Pregnancy.

Author: Ayesha A. Motala
Editors: Aslam Amod and Joel A. Dave

References

1. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-553.
2. American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetesd2016. Diabetes Care 2016; 39(Suppl.1):S13–S22
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014; 37(Suppl.1): S81–S90

4. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: http://www.who.int/diabetes/publications/report-hba1c_2011.pdf. (accessed 25 January 2016)
5. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediatehyperglycaemia:http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf (accessed 21 January 2016)
6. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013; 37(suppl 1):S1-S212.
7. Smiley D, Chandra P, Umpierrez GE. Update on diagnosis, pathogenesis and management of ketosis-prone Type 2 diabetes mellitus. Diabetes Manag. 2011;1(6):589-600. doi:10.2217/dmt.11.57.
8. Hope S V., Wienand-Barnett S, Shepherd M, et al. Practical Classification Guidelines for Diabetes in patients treated with insulin: a cross-sectional study of the accuracy of diabetes diagnosis. Br J Gen Pract. 2016;66(646):e315-e322. doi:10.3399/bjgp16X684961.
9. Anık A, Çatlı G, Abacı A, Böber E. Maturity-onset diabetes of the young (MODY): An update. J Pediatr Endocrinol Metab. 2015 Mar;28(3-4):251-63. doi: 10.1515/jpem-2014-0384.
10. Stenstrom G, Gottsater A, Bakhtadze E, Berger B, Sundkvist G. Latent Autoimmune Diabetes in Adults: Definition, Prevalence, -Cell Function, and Treatment. Diabetes. 2005;54(Supplement 2):S68-S72. doi:10.2337/diabetes.54.suppl_2.S68.
11. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, Shattock M, Bottazzo GF, Holman R, UK Prospective Diabetes Study (UKPDS) Group: UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. Lancet350 :1288 –1293,1997
12. World Health Organization. Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy. Geneva: World Health Organization; 2013. Available from: http://www.ncbi.nlm.nih.gov/books/NBK169024/

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 3: Screening and diagnosis of type 2 diabetes and intermediate hyperglycaemia

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations
The diagnosis of diabetes is confirmed: a. In patients *with symptoms* of hyperglycaemia (polyuria, polydipsia, blurred vision, weight loss) or metabolic decompensation (diabetic ketoacidosis or hyperosmolar non-ketotic state), when *any one single test* confirms that the: ◦ Random plasma glucose is ≥ 11.1 mmol/L ◦ Fasting plasma glucose is ≥ 7.0 mmol/L ◦ HbA_{1c} is ≥ 6.5% ◦ 2-hour post-load glucose is ≥ 11.1 mmol/L. However, a GTT is rarely needed in this category of patient. b. In an *asymptomatic individual*, when *any one* of the following tests, *repeated* on separate days within a 2 week period confirms that the: ◦ Fasting plasma glucose is ≥ 7.0 mmol/L ◦ 2 hr-post load glucose (OGTT) is ≥ 11.1 mmol/L ◦ HbA_{1c} is ≥ 6.5% If the diagnosis of diabetes is not confirmed with the repeated test, institute lifestyle modification and retest in 3 to 6 months.
HbA_{1c} can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.
Bedside or point-of-care devices (for glucose or HbA1c) must not be used to diagnose diabetes.
HbA1c of 6.5% is recommended as the cut-point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. A glucose based measurement is desirable in individuals with HbA1c values close to the diagnostic cut-point (e.g. 6.0 to 6.4%).
The diagnosis of type 2 diabetes is confirmed when all other causes of diabetes are reasonably excluded (refer to Chapter 2).
Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are categories of intermediate hyperglycaemia that identify individuals at risk for future diabetes and cardiovascular disease. IFG and IGT are modifiable risk factors. Refer to Chapter 25 for management of these risk factors.
Impaired fasting glucose is present when 2 consecutive tests performed on different days confirm that the fasting plasma glucose is 6.1 to 6.9 mmol/L, in the absence of diabetes and impaired glucose tolerance by other tests.
Impaired glucose tolerance is present when 2 consecutive tests performed on different days confirm that the 2-hour post-load plasma glucose is 7.8 to 11.0 mmol/L, in the absence of diabetes by any other test.
Screening for type 2 diabetes: Screen all overweight adults at any age if they have at least one other risk factor for diabetes. For all other adults, start screening for diabetes at age 45. The frequency of rescreening for diabetes depends on individual risk and can range from 3 months (e.g. the obese individual with IGT and multiple other risk factors for diabetes) to 3 years (e.g. the normal-weight individual with no risk factors for diabetes). The preferred screening test for high-risk individuals is the OGTT as it is more sensitive and is the only method for detecting impaired glucose tolerance.

3.1 Introduction

There have been no changes to the diagnostic criteria for the diagnosis of diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) since the SEMDSA 2012 Guideline. The different recommended diagnostic cut-points for IFG from the American Diabetes Association (ADA) [5.6 to 6.9 mmol/L] and the World Health Organisation (WHO) [6.1 to 6.9 mmol/L] was reconsidered. The WHO position is retained and endorsed. The categorisation of individuals with non-diabetic but abnormal HbA_{1c} (5.7 to 6.4%) was also reconsidered. The WHO position, that there is insufficient

Table I: interpretation of tests used for screening and diagnosis of diabetes

Fasting plasma glucose[a] (FPG)[a] (mmol/L)	<5.6 Diabetes excluded	6.0 - 6.9 Impaired fasting glucose[e]	≥ 7.0 Diabetes[e]
2hr-plasma glucose (2-hr PG)[b] (mmol/L)	<7.8 Normal glucose tolerance	7.8 - 11.0 Impaired glucose tolerance[e]	≥ 11.1 Diabetes[e]
Glycated haemoglobin A_{1c} (HbA_{1c})[c] (%)	<6.5 Inconclusive[f]		≥ 6.5 Diabetes[e]
Random plasma glucose (RPG)[d] (mmol/L)	<5.6 Diabetes excluded	5.6 - 11.0 Inconclusive[f]	≥ 11.1 Diabetes[e]

[a] Fasting is defined as no caloric intake for at least 8 hours.

[b] 2-h PG is measured during an oral glucose tolerance test (OGTT); The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in 250 ml water and ingested over five minutes.

[a,b] Glucose should be measured immediately after collection by near-patient testing, or if a blood sample is collected, plasma should be immediately separated, or the sample should be collected into a container with glycolytic inhibitors and placed in ice-water until separated prior to analysis.

[c] HbA_{1c} : refers to glycated haemoglobin measurement performed using a DCCT standardised assay and an NGSP certified laboratory, in the absence of conditions that preclude its accurate measurement.

[d] Random (casual) is defined as any time of day, without regard to time of last meal. RPG should only be performed in patients with classic symptoms (polyuria, polydipsia, weight loss) or those with hyperglycaemic crises (diabetic ketoacidosis or hyperosmolar non-ketotic state). It is not a recommended screening test for asymptomatic individuals. A RPG < 11.1 mmol/L does not exclude the diagnosis of diabetes.

[e] In non-pregnant individuals with classic symptoms of diabetes or hyperglycaemic crises, a single abnormal test result confirms the diagnosis of diabetes. The diagnosis of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or diabetes in asymptomatic individuals must be confirmed with a second measurement using the same test method as soon as is convenient.

[f] FPG or 2-h PG should be measured in those individuals with inconclusive results from RPG or HbA_{1c}.

Note: if two or more test methods yield discordant results the individual is classified with the more abnormal disorder of glucose regulation. The test with the more abnormal result will need to be repeated on a different day in asymptomatic individuals.

evidence at this time make any firm recommendations for the classification of this category of abnormal HbA_{1c}, is endorsed. A glucose-based measurement is recommended for risk stratification in these individuals. The use of the term prediabetes to describe the high-risk categories of intermediate hyperglycaemia (IFG and IGT) was debated; although inaccurate and not ideal, the term prediabetes has become entrenched in medical literature, and it is thought to improve communication with professionals and patients regarding diabetes risk. The term prediabetes is therefore an acceptable alternative for IFG and/or IGT.

3.2 Interpretation of diagnostic tests for diabetes and other categories of glycaemia

Plasma glucose, (both fasting and 2-h PG) is a continuous variable that predicts premature mortality and increased risk of microvascular and cardiovascular complications. The current diagnostic criteria for diabetes distinguishes a group of individuals with significantly increased risk. Normoglycaemia is defined arbitrarily by glucose values that carry a low risk (not zero risk) of cardiovascular complications and future progression to diabetes. IFG and IGT define intermediate hyperglycaemia and risk i.e. glucose values that are associated with a higher risk of cardiovascular complications and progression to diabetes than normoglycaemia, but a lower risk of microvascular and cardiovascular complications than diabetes.[5] Unlike diabetes, IFG and IGT are not clinical entities but rather risk factors for future diabetes and adverse outcomes. They are by no means the only risk factors for future diabetes and cardiovascular complications, and ideally these categories of intermediate hyperglycaemia will be superceded by an overall risk assessment (which will include glucose as a continuous variable) for diabetes and cardiovascular disease.[5]

The diagnostic tests, criteria and cut-points for the diagnosis of diabetes mellitus (diabetes) and categories of intermediate hyperglycaemia (categories of increased risk for diabetes) are outlined in Table I.[1-6] The footnotes in Table I are extremely important. The same tests are used to diagnose and screen for diabetes and to detect individuals with intermediate hyperglycaemia (IFG and IGT).

3.3 Diagnosis of diabetes

Diabetes may be identified anywhere along the clinical spectrum: in apparently low-risk asymptomatic individuals who happen to have glucose testing; in those tested based on diabetes risk assessment; and in symptomatic patients. Diabetes can be diagnosed based on the plasma glucose criteria, either the fasting plasma glucose (FPG), the 2-h plasma glucose (2-h PG) value after a 75 g oral glucose tolerance test (OGTT), a random plasma glucose in symptomatic individuals, or the HbA_{1c} criteria.[1-6] No one test is preferred over another for diagnosis.[2] For clinical purposes, the diagnosis of diabetes should always be confirmed by repeating the test on another day, preferably, the same test, unless there is unequivocal hyperglycaemia with acute metabolic decompensation or classic (obvious) symptoms (i.e. polyuria, polydipsia and weight loss). The diagnosis of diabetes must be based on formal laboratory testing and not point-of-care or bedside instruments (e.g. glucose reflectance meters or single-use HbA_{1c} kits). For glucose-based diagnosis, laboratory venous plasma glucose is preferred. Capillary blood glucose measurements should only be used for diagnosis in the rare event that laboratory measurements are unavailable. In this

event, if the reflectance meter is not pre-calibrated to convert capillary glucose to plasma glucose, the plasma glucose value will need to be derived using the following conversion factor: Plasma glucose (mmol/l) = 0.102 + 1.066 x capillary blood glucose.

3.3.1 HbA1c vs. plasma glucose for diagnosis (refer to Appendix 3)

The HbA1c test used for diagnosis of diabetes must meet the following conditions:[2-4, 6]

- The test method must meet stringent quality-assurance criteria.
- The assay must be standardised to criteria aligned to international reference values (i.e. NGSP certified).
- The assay must be standardised or traceable to the DCCT reference assay
- There must be no conditions present which preclude the accurate measure of HbA1c.

Point of care HbA1c assays for diagnostic purposes is not recommended, because although some such assays may be NGSP certified, proficiency testing is not mandated for performing the test. For a complete list of laboratories that are NGSP certified, the reader is referred to the NGSP website.[7]

HbA1c has some advantages compared with plasma glucose-based criteria (FPG and OGTT), including greater convenience (fasting not required), greater pre-analytic stability, and less day-to-day perturbations during stress and illness. However, these advantages may be offset by the following: lower sensitivity (of HbA1c) at the designated cut-point, greater cost, limited availability in certain developing countries and imperfect correlation between HbA1c and average glucose in certain individuals. National Health and Nutrition Examination Survey (NHANES) data from the USA indicate that an HbA1c cut-point of $\geq$ 6.5% (48 mmol/mol) identifies one third fewer cases of undiagnosed diabetes than a FPG cut-point of $\geq$ 7.0 mmol/l.[8]

It is important to take age, race/ethnicity, anaemia, haemoglobinopathy, and other states of increased red cell turnover into consideration when using HbA1c to diagnose diabetes. In conditions associated with increased red cell turnover, such as pregnancy (2nd and 3rd trimester), recent blood loss or transfusion, erythropoeitin therapy, or haemolysis, only blood glucose criteria should be used to diagnose diabetes.[2-4]

Regarding the plasma glucose/glucose-based criteria, both FPG and 2h-PG may be used to diagnose diabetes. The concordance between FPG and 2h-PG tests is imperfect, as is the concordance between HbA1c and either glucose-based test. Several studies have confirmed that, compared with FPG and HbA1c cut-points, the 2-h PG value diagnoses more people with diabetes.[2-3]

3.3.2 Diagnosis in symptomatic individuals and unequivocal hyperglycaemia

In patients who have the classic symptoms of hyperglycaemia (polyuria, polydipsia and weight loss), or unequivocal hyperglycaemia i.e. hyperglycaemic crisis (diabetic ketoacidosis or hyperosmolar non-ketotic hyperglycaemia) a single abnormal test is sufficient to confirm the diagnosis of diabetes. The OGTT can result in severe hyperglycaemia and a random plasma glucose will usually be adequate in this clinical situation. Note that even severe hyperglycaemia detected under conditions of acute infective, traumatic, cardiovascular or other stress including corticosteroid therapy, may be transitory and should not be regarded as diagnostic of diabetes until confirmed subsequently.

3.3.3 Diagnosis in asymptomatic individuals or doubtful hyperglycaemia

In asymptomatic individuals and in those where there is doubt about the presence of persistent hyperglycaemia, the diagnosis of diabetes (or other categories of intermediate hyperglycaemia) should *not* be based on a single abnormal test result. It is advisable to perform *either* a glucose-based test (fasting or 2-h PG), *or* the HbA1c test. If the test is abnormal, then the *same* test must be repeated on another day (preferably within 2 weeks) to confirm the diagnosis.

In the event that both a glucose-based test and the HbA1c test are measured, if both are "diagnostic" for diabetes, then the diagnosis of diabetes is confirmed. If only one of these tests is abnormal, a second abnormal result of the same testing method is required to confirm the diagnosis of diabetes on a different day, preferably within two weeks. Should the repeat test not confirm diabetes, the test should then be repeated after 3-6 months.[2-4]

A test result below the diagnostic threshold for diabetes does not exclude the diagnosis of diabetes. So although the diagnostic cut-point for fasting plasma glucose is 7.0 mmol/L and 6.1 mmol/l for diabetes and IFG respectively, one can only exclude the diagnosis of diabetes if the fasting plasma glucose is $\leq$ 5.6 mmol/l. The level of HbA1c below which the diagnosis of diabetes is excluded is not known [the American Diabetes Association (ADA) uses a cut-point of < 5.7% but the World Health Organisation (WHO) report does not endorse this]. This raises a dilemma in individuals in whom the HbA1c test result is close to, but does not exceed, the diagnostic cut-point of 6.5%. SEMDSA recommends a glucose-based measurement (FPG or 2-h PG) for high-risk individuals whose HbA1c is abnormal but not diagnostic of diabetes (refer to Chapter 2 for risk factors).

3.4 Diagnosis of intermediate hyperglycaemia/ categories of increased risk for diabetes (IFG and IGT)

Table I outlines the diagnostic criteria for IFG and IGT. By definition these categories of glycaemia mandate a FPG or OGTT for diagnosis. As is the case with diabetes, there is also considerable discordance between the FPG and 2-h PG test in identifying intermediate hyperglycaemia. Nevertheles,s a fair proportion of individuals will have both IFG and IGT.[5]

Glucose-based measurements have variable reproducibility which emphasises the need for repeat testing to confirm the diagnosis. Approximately 40-60% of individuals with IFG and or IGT will have confirmatory tests on retesting, about 10% will meet the diagnostic criteria for diabetes and the rest will revert to normal.[5] The reproducibility of fasting glucose is somewhat better than the 2-h PG.

The risk of progression to diabetes varies among ethnic groups. A meta-analysis of prospective studies showed that the annual incidence of diabetes in individuals with IFG and IGT was 6-9% and 4-6% respectively. The incidence in persons with both IFG and IGT was significantly higher at 15-19%/yr.[13] In South African Indians with IGT, the annual incidence of diabetes was found to be 12.6% per year over four years.[14] Refer to "Chapter 27: Prevention and delay of type 2 diabetes" for a discussion on the management of IFG and IGT.

3.4.1 IFG, IGT and prediabetes – the controversies

(Optional reading)

The 2011 WHO report only recommended an HbA_{1c} cut-point (≥ 6.5%/48mmol/mol) for the diagnosis of diabetes and emphasized that a value < 6.5% does not exclude diabetes diagnosed using glucose tests. The report concluded that there was insufficient evidence at the time to make any formal recommendation on the interpretation of HbA_{1c} level < 6.5%.[4] That report also endorsed the previous WHO recommendations[1,5] of retaining the cut-point plasma glucose for IFG at 6.1 mmol/L vs. the 2003 ADA recommended cut-point of 5.6 mmol/l[2,3]; the reasons included lack of evidence of any benefit in reducing adverse outcomes or progression to diabetes and the possible impact on individuals and health systems with the significant increase in IFG prevalence.[4]

The ADA has since 2010, recommended that an HbA_{1c} 5.7-6.4% (39-46 mmol/mol) can be used to identify categories at increased risk for diabetes in addition to IFG and IGT, and uses the term prediabetes to describe these three categories; the argument being that for all these tests, the risk continues, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.[2,3,9] In addition, the ADA has recommended screening individuals with risk factors for the purpose of detecting prediabetes (as opposed to only screening to detect diabetes). The counter argument is that there is no universal lower level of either glucose or HbA_{1c} that eliminates risk.

The question needs to evolve from "is a certain level of glucose associated with risk" to " is intervention at that level likely to be beneficial, cost-effective and affordable". Regarding IFG, lowering the FPG threshold to 5.6 mmol/l means that ~30% of people would be classified as having prediabetes. There is little evidence that this is very useful. The same is true for lowering the HbA_{1c} threshold because as the threshold goes lower than 6.0 %, one is on the steep section of the normal distribution and many people get labelled. In addition HbA_{1c} in the range 5.7 to 6.4% appears to identify a much smaller population of prediabetes than does IFG or IGT, it includes people who do not IFG or IGT, IFG and IGT are stronger predictors of CVD than HbA_{1c} and intervention studies in prediabetes have included patients based on IGT (predominantly) and IFG. There have been no prospective intervention studies based on HbA_{1c}.[5,10,11]

The question to ask is what is the purpose of labelling someone with prediabetes? What are you going to do on the basis of that knowledge? How many people can you afford to offer individual prevention to? Using this logic, one would probably keep the thresholds high. In the case of FPG there is no evidence that people in the range 5.5-6.1 mmol/L are at substantial cardiovascular risk. There is also no trial evidence of benefit of lifestyle intervention; and the population is large with an unknown cost-benefit ratio for any intervention.

SEMDSA's position is that the cut point of FPG and IFG should remain at 6.1 mmol/l and that the previous position of not recommending HbA_{1c} for intermediate hyperglycaemia should be retained, until there is substantial evidence from prospective studies that there is a defined threshold of HbA_{1c} above which there is increased/absolute risk of progression to diabetes or development of its complications, and until it can be shown that no individual with HbA_{1c} < 6.5% has diabetes. The same is true for screening for IFG and IGT i.e. until there is further evidence, screening for intermediate hyperglycaemia should not be recommended. It is also important that serum insulin should not be used for diagnosis of intermediate hyperglycaemia.

The use of the term prediabetes for individuals with IFG/IGT is problematic because it implies that all of these individuals will develop diabetes, and that those who do not meet the criteria for prediabetes will not, neither of which is true. For example, it ignores people with other non-glucose based risk factors such as the woman with a history of gestational diabetes, whose risk of diabetes is quite high (20-60%) over the five to ten years after pregnancy.[12] Nevertheless the term prediabetes has become sufficiently entrenched in medical and lay literature so as not to be ignored or discarded; a PubMed search yields more literature for the search term "prediabetes" than it does for "intermediate hyperglycaemia" The term prediabetes also facilitates an easier conversation with professionals and patients to help understand the high risk status. If the term prediabetes is used, it should be confined to IFG and IGT, must not include HbA_{1c} and those using the term must not ignore the risk of people who do not have intermediate hyperglycaemia.

3.5 Screening for type 2 diabetes in adults

As described above, the distinction between diagnostic testing and screening for diabetes is somewhat blurred. The same tests are used for "screening" and for diagnosis. Diabetes may be identified anywhere along a spectrum of clinical presentations, ranging from low-risk individuals who happen to have glucose testing incidentally (*random screening*), to individuals identified as having a high risk for diabetes during routine consultations for unrelated health matters (*opportunistic screening*), to those who are deliberately identified and tested because of their high risk status (*targeted screening*). The spectrum then extends to the higher-risk individual with clinical features suggestive of diabetes (e.g. obese adult with recurrent urinary infections and nocturia) whom the provider tests because of a high suspicion of diabetes, and finally to the patient with classic symptoms or metabolic decompensation. The latter two scenarios would be considered diagnostic testing.

Because of the need for follow-up, screening should only be carried out within the health care setting. Community screening outside a healthcare setting (e.g. fun days, shopping centres) is not recommended, because individuals with abnormal (positive) tests may not seek or have access to appropriate follow-up testing and care. Or, for those who test negative, there may be

Table II: Criteria for screening for type 2 diabetes in asymptomatic adults [1-3, 5]

Indications	1. High risk individuals: All adults (any age) who are overweight (BMI> 25 kg/m^2 or > 23 kg/m^2 in Asians), plus one or more additional risk factors[b]: • Physical inactivity • Hypertension [Blood pressure (BP) ≥ 140/90 mmHg] or treatment for hypertension • First degree relative with diabetes • Dyslipidaemia[c] • Polycystic ovarian syndrome • High-risk race/ethnicity (Asian Indian, Coloured) • Cardiovascular disease history • Gestational diabetes or baby > 4 kg • Previous IFG or IGT • Other conditions associated with insulin resistance (severe obesity, acanthosis nigricans) 2. If no risk factors: Age ≥ 45 years
Frequency	At three-year intervals, if normal More frequently, based on initial result and risk status
Test method	FPG, 2-h PG (OGTT) or $HBA_{1c.}$ The OGTT is the preferred test in high risk individuals.

[a] Only to be done within the healthcare setting
[b] Risk factors for future diabetes
[c] Serum high-density lipoprotein (HDL) cholesterol < 0.90 mmol/l, or triglycerides > 2.82 mmol/l

failure to ensure appropriate repeat testing. Such screening may also be poorly targeted, i.e. may fail to reach groups most at risk, and inappropriately test those at low risk (the "worried well") or those already diagnosed.

Similarly, random screening for all adults is not recommended until after the age of 45years. The indications for targeted and opportunistic screening are described in Table II.

3.5.1 Screening for diabetes vs. screening for diabetes and prediabetes

In 2016, the ADA[2] recommends guidelines for screening tests for both type 2 diabetes and prediabetes in asymptomatic adults (vs. screening tests only for diabetes). This has been discussed in Section 3.3.1. SEMDSA advocates screening for the detection of diabetes; individuals identified with IFG/IGT during this process can be managed appropriately. In any case the risk factors for prediabetes are the same as the risk factors for diabetes.

Author: Ayesha A. Motala
Editor: Aslam Amod

References

1. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-553.
2. American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetesd2016. Diabetes Care 2016; 39(Suppl. 1):S13–S22.
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl. 1):S81–S90.
4. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: http://www.who.int/diabetes/publications/reporhba1c_2011.pdf.(accessed 25 January 2016).
5. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf (accessed 21 January 2016).
6. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013;37(suppl 1):S1-S212.
7. http://www.ngsp.org/certified.asp (accessed 13 February 2012).
8. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988-2006. Diabetes Care. 2009;32:1327-1334.
9. American Diabetes Association: Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010; 33(Suppl.1):S62–S69.
10. Buysschaert M, Medina J-L, Buysschaert B, Bergman M. Definitions (and Current Controversies) of Diabetes and Prediabetes. Curr Diabetes Rev. 2015;12(1):8-13. doi:10.2174/1573399811666150122150233.
11. Bonora E, Tuomilehto J. The Pros and Cons of Diagnosing Diabetes With A1C. Diabetes Care. 2011;34(Supplement_2):S184-S190. doi:10.2337/dc11-s216.
12. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379(9833):2279-2290. doi:10.1016/S0140-6736(12)60283-9.
13. Gerstein HC, Santaguida P, Raina P, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: A systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract. 2007;78(3):305-312. doi:10.1016/j.diabres.2007.05.004.
14. Motala AA, Omar MAK, Gouws E. High Risk of Progression to NIDDM in South-African Indians with Impaired Glucose Tolerance. Diabetes. 1993;42(4):556-563. doi:10.2337/diab.42.4.556.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Chapter 4: Organisation of Diabetes Care

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Patients with diabetes should be seen by dedicated staff at a clinic/facility with adequate space and resources (equipment and medication)	C
The diabetes consultation should be a structured one. The use of standardised diabetes consultation templates is encouraged to ensure that essential assessments / processes of care are not omitted.	C
At each visit the patient should have a history taken, undergo a clinical examination and have blood taken for biochemical evaluation.	
The complexity of each will be dependent on whether it is an initial consultation, follow-up consultation or an annual review	C

Requirements for a Diabetic Clinic

- Dedicated, appropriately trained staff
- Adequate space:
  - For individual consultation
  - For group education
- Protocols covering:
  - Screening
  - Regular care, including referrals
- Equipment:
  - Tape measure (waist circumference)
  - Scale
  - Height measure
  - Accurate sphygmomanometers, with two cuff sizes
  - Monofilament and 128 Hz tuning fork
  - Glucometers in good working order
  - HbA_{1c} testing equipment, to enable testing on site
  - Educational material
- Regular supply of medication
- Register with recall system for non-attenders
- Annual audits of:
  - Numbers of patients receiving designated processes of care
  - Numbers of patients reaching targets for glycaemia, blood pressure (BP) and lipids
  - History, clinical examination, investigations: What to do when

History	Initial	3-6 monthly visit	Annually
Symptoms of hyperglycaemia, and duration of symptoms	X	X	X
Relevant family history	X		X
Other risk factors (e.g. gestational diabetes, high birthweight)	X		X
Relevant medical history			
Co-morbid conditions	X		X
Symptoms of complications	X	X	X
Cardiovascular, neurological, bladder function, sexual function (i.e. erectile dysfunction), feet, visual, infection			
Drugs			
Current	X		X
Side-effects and adherence	X	X	X
Allergies	X		X
Hypoglycaemic symptoms	X	X	X
Vaccinations			
Pneumococcal (date)	X		X
Influenza (date)	X		X
Lifestyle			
Weight history	X	X	X
Physical activity	X	X	X
Eating pattern	X	X	X
Smoking	X	X	X
Alcohol	X	X	X

Psychosocial			
Occupation	X		X
Family and community support	X		X
Depression	X	X	X
Home monitoring chart (if relevant)	X	X	X

EXAMINATION	**Initial visit**	**3-6 monthly visit**	**Annually**
Weight	X	X	X
Height	X		X
BMI (kg/m^2)	X	X	X
Waist circumference (cm)	X	X	X
Blood pressure	X	X	X
Feet - detailed examination[§]	X		X
Monofilament assessment	X		X
Vibration sensation assessment	X		X
Ankle jerks	X		X
Evaluation for peripheral arterial disease	X		X
Oral cavity			
- dental caries	X		X
- gum disease	X		X
Eye examination			
-Visual acuity	X		X
- Retinal examination*	X		X
Cardiovascular examination	X		X
Injection sites if appropriate	X	X	X

§ See Chapter 21
*The preferred method for screening for retinopathy is retinal imaging using non-mydriatic fundus photography (the images can be interpreted remotely by those with the expertise); dilated fundoscopy can be used in the absence of a retinal camera by those clinicians who have the necessary expertise to diagnose diabetic retinopathy, and in patients where dilatation of the pupil will not hamper driving or returning to work.

Investigations	**Initial visit**	**3-6 monthly visit**	**Annually**
Blood			
Glucose	X		
HbA$_{1c}$	X	X	X
Lipids (TC, HDLc, TG, LDLc)	X		X
Creatinine and calculation of eGFR	X		X
Potassium	X		X
HIV	X		
Urine			
Dipstix			
Glucose	X	X	X
Ketones	X	X	X
Protein	X	X	X
Albumin/creatinine ratio	X		X
ECG	X		X
Continuous glucose monitoring*	X	X	X

*Refer to Chapter 8

Other important tasks	**Initial visit**	**Every visit**	**Annually**
Diabetes educator*	X	X	X
Education: Self-management and lifestyle adjustment, including smoking cessation	X	X	X
Setting goals	X	X	X
Preconception counselling and family planning	X	X	X
Medication revision/adjustment	X	X	X
Immunisations	X		X
Testing for autonomic neuropathy	X		X

*Any healthcare worker who has completed, with competence, a South African Nursing Council or SEMDSA-approved diabetes educators course.

Authors: Naomi S. Levitt and Joel A. Dave

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 5: Diabetes self-management education and support

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
People living with diabetes should be offered structured diabetes education at diagnosis and this should be consolidated at regular intervals.	B
Diabetes self-management education and support (DSME/S) should be patient-centred, respectful and receptive to individual needs and values; and non-discriminatory towards cultural, ethnic language, socio-economic and educational differences.	B
DSME/S should incorporate cognitive-behavioural interventions, the practical application of knowledge and aim to increase patient participation in decision making.	B
DSME/S should be managed by accredited health care professionals who have been appropriately trained in the execution of evidence-based principles.	B
Trained community health workers should provide education through home visits, create awareness and encourage adherence.	C
SEMDSA recommends that DSME, provided by health professionals in a format endorsed by SEMDSA and DESSA, should be reimbursed according to NHRPL guidelines.	C

5.1 Introduction

Diabetes is a heterogenous condition and adequate management thereof requires input from various role players. It requires continuous support from a multidisciplinary team of health care providers (HCP) and constant effort in assisting people living with diabetes to make the right choices around food, medication, and exercise.[1] People living with diabetes, their caregivers and families should be skilled in numerous self-management activities in order to manage this effectively.[1] The ultimate goal is to empower people living with diabetes to be more engaged and informed about the condition. It is crucial for successful self-management of diabetes to ensure that treatment and quality of life goals are achieved.[1] DSME has been shown to improve glycaemic control which is one of the strongest predictors of disease progression and the development of diabetes complications.[2,3] It is the educator's role to assist with this endeavour and make it as trouble-free as possible.

The words of Elliot P. Joslin still holds true: "The person with diabetes who knows the most lives the longest."[4]

5.2 Defining Diabetes-Self Management Education and Support (DSME & DSMS)

DSME is the ongoing process of facilitating knowledge, skill, ability and motivation for diabetes self-care that involves active participation of the people living with diabetes. It integrates the needs, goals and life experiences of the people and is grounded on evidence-based principles. DSME is not a once-off event but a lifelong necessity starting at diagnosis.[1,5] DSME/S is one of the core elements of the Care Model that is advocated for people living with a chronic condition. DSME content should be patient centred, considerate of cultural background and practices, tradition, religion, literacy levels and family values, as all of these factors impact on the motivation for learning.[6-8] Four crucial time points where DSME is advocated: at diagnosis, annually, when new complicating factors e.g. pregnancy arise and when transition into different life stage occurs.[1] Diabetes education algorithms defining these four time points and including the topics that need coverage are available at *http://professional.diabetes.org/*

5.3 Role of the diabetes educator

The joint position statement on DSME of the Diabetes, Diabetes Educators and the Academy of Nutrition and Dietetics of America advocate that the person responsible for providing the DSME should be a health professional (e.g. nurse, dietician or pharmacist) who is trained by means of an accredited programme. The Diabetes Educator (DE) should meet specific competency and ongoing education requirements.[1,6] The DE should have good interpersonal skills and must prioritise motivational interview techniques to cultivate patient commitment and participation.[21] The primary DE may support and educate other health carers such as community health workers, peers and family-members with DSME/S. Diabetes self-management and education by trained health care workers are equally effective in improving glycaemic control, self-care activities and quality of life.[2,9-12]

5.4 Specific components of DSME/S

5.4.1 Duration of sessions

Better outcomes are directly linked to the amount of time spent on education.[1] In a South-African community based programme a 5% weight loss and 1% reduction in HbA_{1C} was achieved after just four (4) education sessions of 20-60 minutes each.[13]

5.4.2 Methods towards effective DSME/S

The person living with diabetes (and family members) should be the centre of the care model encouraging active partnership with health care professionals and all decision making must be guided by the values of the person with diabetes.[14] Interactive interventions such as cognitive behavioural techniques, joint decision making, problem solving skills and the generation of action plans towards realistic patient-chosen goals should be fostered. The identification and addressing of barriers to self-care are just some of the steps to successful DSME.[1,15] Table I gives examples of questions to ensure a patient centred approach.

Table I. Examples of questions to ensure a patient centred approach[15]

- How is diabetes affecting your daily life and that of your family?
- What questions do you have?
- What about your diabetes is the hardest part right now, or causing you the most concern, or is the most worrisome to you?
- How can we best help you?
- What is one thing you are doing or can do to better manage your diabetes?

5.4.3 Essential components of DSME

Successful diabetes care includes a systematic approach with adequate coverage of the essential components of DSME as summarised by the ADA's standards of medical care 2017. Refer to Table II.

Table II. Components of DSME as per ADA standards of medical care

- Healthy lifestyle choices (healthy eating, physical activity, tobacco cessation, weight management, and effective strategies for coping with stress)
- Disease self-management (taking and managing medications and, when clinically appropriate, self-monitoring of glucose and blood pressure)
- Prevention of diabetes complications (self-monitoring of foot health; active participation in screening for eye, foot, and renal complications; and immunisations)
- Identification of self-management problems and development of strategies to solve those problems, including self-selected behavioural goal setting.

5.5 Efficacy of DSME

DSME improves haemoglobin A1c (A1c) by up to 1%.[1,2] It is proven to be cost-effective due to the reduction in hospital admissions and lifetime cost of diabetes complications.[16-19] A summary of the clinical, behavioural and psychological areas of diabetes that are positively impacted on are listed in Table III.[1,5,14]

5.6 The role of technology in DSME/S

The internet, web-based education, cell phones, emails, automatic reminders and telephonic education are effective and efficient ways of providing DSME.[5,20] These modalities provide a way to overcome barriers such as distance as well as the resource limitations in terms of sufficient certified DE's.[20]

Table III. Benefits of DSME

- Improved glycaemic control
- Reduction in total health care cost
- Enhancing knowledge
- Self-care behaviour and self-efficacy enhanced
- Likelihood of lifestyle adherence and weight maintenance
- Risk identification of cardiovascular events and risk factors
- Improves quality of life and healthy coping

5.7 Remuneration and reimbursement for DSME

Healthcare professionals who provide structured DSME in a format approved by DESSA and SEMDSA must be reimbursed by third-party payers as it is a core component of diabetes management, and has the potential to improve outcomes and reduce costs.[14] Reimbursement should follow recommendations as per NHRPL guidelines and should be updated annually.

Conclusion

Adequate and ongoing DSME is an integral component of diabetes care. It should use evidence-based strategies and promote the practical application of knowledge.

Authors: Razana Allie, Hamish van Wyk, Ankia Coetzee and Lourentia van Wyk.
Editors: Zaheer Bayat and Aslam Amod.

References

1. Powers MA, Bardsley J, Cypress M, Duker P, Funnell MM, Fischl AH, Maryniuk MD, Siminerio L, Vivian E. Diabetes self-management education and support in type 2 diabetes a joint position statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. The Diabetes Educator. 2015 Aug 1;41(4):417-30.
2. Chrvala CA, Sherr D, Lipman RD. Diabetes self-management education for adults with type 2 diabetes mellitus: A systematic review of the effect on glycemic control. Patient education and counseling. 2016 Jun 30;99(6):926-43.
3. Pani LN, Nathan DM, Grant RW. Clinical predictors of disease progression and medication initiation in untreated patients with type 2 diabetes and A1C less than 7%. Diabetes Care. 2008 Mar 1;31(3):386-90.
4. Levetan C. Adding a daily dosage of diabetes wisdom to your prescription. Diabetes Spectrum. 2001 Aug 1;14(3):163-7.
5. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Self-Management Education. Canadian Journal of Diabetes 2013;37(suppl 1):S26-S30
6. Haas L, Maryniuk M, Beck J, Cox CE, Duker P, Edwards L, Fisher E, Hanson L, Kent D, Kolb L, McLaughlin S. National standards for diabetes self-management education and support. The Diabetes Educator. 2012 Sep;38(5):619-29.
7. American Diabetes Association. 1. Promoting Health and Reducing Disparities in Populations. Diabetes Care. 2017 Jan 1;40(Supplement 1):S6-10.
8. American Association of Diabetes Educators. AADE guidelines for the practice of diabetes self-management education and training (DSME/T). The Diabetes Educator. 2009 Nov 1;35(3 suppl):85S-107S.
9. Lorig K, Ritter PL, Villa F, Piette JD. Spanish diabetes self\-management with and without automated telephone reinforcement. Diabetes Care. 2008 Mar 1;31(3):408-14.
10. Lorig K, Ritter PL, Villa FJ, Armas J. Community-based peer-led diabetes self-management a randomized trial. The Diabetes Educator. 2009 Jul 1;35(4):641-51.

11. Smith SM, Paul G, Kelly A, Whitford DL, O'Shea E, O'Dowd T. Peer support for patients with type 2 diabetes: cluster randomised controlled trial. Bmj. 2011 Feb 15;342:d715.
12. Babamoto KS, Sey KA, Camilleri AJ, Karlan VJ, Catalasan J, Morisky DE. Improving diabetes care and health measures among hispanics using community health workers: results from a randomized controlled trial. Health Education & Behavior. 2009 Feb;36(1):113-26.
13. Mash B, Levitt N, Steyn K, Zwarenstein M, Rollnick S. Effectiveness of a group diabetes education programme in underserved communities in South Africa: pragmatic cluster randomized control trial. BMC family practice. 2012 Dec 24;13(1):126.
14. American Diabetes Association. 4. Lifestyle Management. Diabetes Care. 2017 Jan 1;40(Supplement 1):S33-43.
15. Funnell MM, Bootle S, Stuckey HL. The diabetes attitudes, wishes and needs second study. Clinical Diabetes. 2015;33:32-36.
16. Healy SJ, Black D, Harris C, Lorenz A, Dungan KM. Inpatient diabetes education is associated with less frequent hospital readmission among patients with poor glycemic control. Diabetes care. 2013 Oct 1;36(10):2960-7.
17. Duncan I, Ahmed T, Li QE, Stetson B, Ruggiero L, Burton K, Rosenthal D, Fitzner K. Assessing the value of the diabetes educator. The Diabetes Educator. 2011 Sep 1;37(5):638-57.
18. Robbins JM, Thatcher GE, Webb DA, Valdmanis VG. Nutritionist visits, diabetes classes, and hospitalization rates and charges. Diabetes care. 2008 Apr 1;31(4):655-60.
19. Brown HS, Wilson KJ, Pagán JA, Arcari CM, Martinez M, Smith K, Reininger B. Cost-effectiveness analysis of a community health worker intervention for low-income Hispanic adults with diabetes. Prev Chronic Dis. 2012 Aug 1;9:E140.
20. Pereira K, Phillips B, Johnson C, Vorderstrasse A. Internet delivered diabetes self-management education: a review. Diabetes technology & therapeutics. 2015 Jan 1;17(1):55-63.
21. Dudley JD. The diabetes educator's role in teaching the diabetic patient. Diabetes Care. 1980 Jan 1;3(1):127-33.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Chapter 6: Medical Nutrition Therapy

SEMDSA Type 2 Diabetes Guideline Expert Committee

SEMDSA 2017 Recommendations for Medical Nutrition Therapy	
Medical nutritional therapy (MNT) has been shown to reduce HbA_{1c} by 0.5 – 2 % in type 2 diabetes	A
Intensive lifestyle interventions, with structured programs focusing on MNT, physical activity and behaviour change with ongoing support, can achieve modest weight loss and improve outcomes in overweight and obese individuals with diabetes and prediabetes. These interventions must be made available to people with type 2 diabetes.	A
There is no ideal percentage of calories from carbohydrates, fat or protein; macronutrient distribution must be individualised.	B
Nutritional approaches must be individualised, based on metabolic goals and a holistic assessment of the individual that is sensitive to, and respectful of, the ethnic, cultural and socio-economic needs of the person. MNT is best delivered by a registered dietitian.	C
Generic nutritional messages (e.g. food plates, handing out pamphlets of "foods allowed and foods to avoid") lack efficacy.	B
The overall quality and sustainability of any dietary approach needs to be considered.	A
A variety of different dietary approaches have been shown to be effective in diabetes management, and current evidence does not suggest that any one single nutrition approach offers greater improvements in glycaemic control or weight loss.	C
Carbohydrate intake (both quality and quantity) should be individualised and guided by the patient's glycaemic control. Carbohydrates from whole grains, legumes, milk, vegetables and fruit should be used instead of refined carbohydrates with added sugar, fats and sodium.	B
The type of fat consumed may be more important than the total fat intake for determining metabolic goals and preventing cardiovascular disease. Monounsaturated fats are preferred to saturated fats. Foods rich in long-chain omega-3 fatty acids, such as fatty fish, nuts and seeds is recommended to prevent cardiovascular disease. The intake of processed meats and fatty red meats should be limited.	B
Intensive lifestyle interventions using a nutritional approach that limits energy from fat (< 30%) and saturated fat (<10%), increases fibre (>15g/1000 kcal) and promotes whole grain, unrefined carbohydrates instead of refined carbohydrates, has proven long-term benefit, efficacy and safety in preventing type 2 diabetes. (Refer to Chapter 27)	A
The long-term safety (cardiovascular and other) of high saturated fat diets, high protein diets or very low calorie diets is not known. This information must be communicated to individuals wishing to adopt this nutritional plan.	C
If the patient decides to consume alcohol it should be in moderation (1 unit per day for women and 2 units per day for men).	C
For general health, sodium intake should be < 2300 mg a day.	B
Do not recommend dietary or vitamin supplements in the absence of proven deficiencies. There is no role for omega-3 supplements.	A

6.1 Introduction

Medical nutritional therapy (MNT) is a vital aspect of both diabetes prevention and diabetes management. A review of the evidence of MNT in the management of-type 2 diabetes has shown an HbA_{1c} reduction of 0.5 to 2%.[1]

The objectives of MNT are to promote the enjoyment of a variety of nutrient dense foods in appropriate portion sizes to:

- Achieve individual glycaemic, blood pressure and lipid goals.
- Achieve and maintain body weight goals
- Delay or prevent complications of diabetes.[1]

Glycaemic control can improve despite no weight loss.[2] Thus, the effects of MNT on glycaemic control goes beyond just weight loss. Despite the former, even with 5-10 % weight loss there are marked improvements in metabolic markers.[3] It should however be noted that these metabolic changes improved even more so with ≥ 15 % weight loss.[3] Due to the improvements in metabolic markers, MNT can be-cost saving.[1]

6.2 An Evidence based Nutritional Approach

Despite the benefits associated with MNT, lack of adherence is a common problem. One of the possible explanations is the approach provided by health professionals. Providing patients with generic nutritional advice does not constitute MNT, but rather describes the control arm of large studies which offer no improvements in metabolic markers.[4] Based on the lack of efficacy associated with generic nutritional messages e.g. food plates, handing out pamphlets of "foods allowed and foods to avoid"- these should be avoided as they are not a substitute for comprehensive MNT. Often vitamins, minerals, herbs and spices are marketed as having clinical benefits for people with diabetes. There is however no evidence to support the use of such products and thus should not be included in the MNT.[1] MNT should consist of regular contact sessions with a registered dietitian (RD) preferably experienced in diabetes management (see Table I).[1] The RD should assess the patient and provide individualized nutrition and behaviour modification education during regular monitoring sessions (see Table 1).

6.3 Different Dietary Approaches for the Management of Diabetes

A variety of different dietary approaches have shown to be effective in diabetes management including, low fat diets, low glycaemic index diets, low carbohydrate diets and Mediterranean diets.[11] Evidence at this point does not suggest that any dietary approach offers greater weight loss or improvements in

Table I: Characteristics of effective MNT [1, 5 -12]

Contact sessions: A series of 3-4 encounters with a RD lasting from 45-90 minutes. This should start at diagnosis and should be completed within 3-6 months. The RD should determine whether additional encounters are needed. At least an annual follow up is recommended for reinforcement, monitoring and evaluation of outcomes.
Assessment: Age, gender, anthropometric measurements, weight history, associated conditions, glycaemic control, nutrition history (24- hour recall & food frequency questionnaire), economic status, lifestyle factors (e.g. work logistics), cultural eating patterns, activity pattern, psychological and cognitive factors impacting on eating behaviour, level of literacy, use of medication and supplements.
Education: Acquiring good nutritional knowledge is the first step towards change. Patients need to develop an understanding of food composition, classification, how nutrients influence weight status, glycaemic control and associated conditions. The former serves to empower patients to make informed food choices. Patients often know what to do, but find it difficult to apply the knowledge practically to achieve positive outcomes. Patients require practical tools such as a personalized, practical eating plan, 7-day-cycle menu, and a shopping list that meets the family's lifestyle, culture, socio-economic status and food preferences. It is important to maintain the pleasure of eating by providing positive messages about food.
Monitoring: Monitoring sessions provide accountability and assist the patient to formulate solutions to their barriers to adherence. The tools dietitians use includes; The 5 A's approach (ask, assess, assist, advice and arrange), goal setting, self-monitoring (food diaries), cognitive restructuring, relapse prevention, incentives, motivational interviewing and modelling. Problem solving together with positive feedback and reinforcement enhance the patient's level of self-efficacy, which is important to create and sustain healthy eating habits.

Table II: Characteristics of a High-Quality Dietary Pattern[1, 14-28]

Food	Nutrient and health benefits / Consequences
High intake of fruit and vegetables: Minimum of 5 portions per day	Increase intake of fibre that enhance satiety, Phyto-nutrients, vitamins and minerals that combat oxidative stress.
Starchy foods should be wholegrain: Corn, barley, pearl-wheat, rolled oats, unrefined maize, wild/brown rice and wholegrain breads	Contain B vitamins, vitamin E and fibre that improve glycaemic control and enhance satiety.
Encourage intake of all types of fish: Especially fatty fish with a high omega 3 content such as sardines	Low saturated fat content, good source of protein, omega 3-fatty acids, selenium, magnesium and vitamin D
Encourage intake of legumes: Soya beans, a variety of dry beans, lentils and chick peas	Promote healthy lipid profile, good source of fibre and protein
Use of low fat sugar free daily products: Low fat plain yoghurt and low fat milk	Provide calcium, vitamin D, and magnesium. Good source of protein with a low saturated fat content
Use of vegetable fats: Such as nuts and seeds, avocado pear, olives, plant oils (canola, olive, sunflower etc. Avoid tropical oils (e.g. coconut and palm cornel oil)	Replace saturated fatty acids in the diet with unsaturated fatty acids tend to reduce the risk of cardiovascular disease (CVD). Tropical oils contain LDL cholesterol raising fatty acids
Reduce intake of commercially hydrogenated fats: Commercially deep fried foods, fast foods and baked items contain high amounts of trans fatty acids	Trans fatty acids raise total and LDL cholesterol, decrease HDL cholesterol and increase inflammation.
Reduce intake of processed meats and fatty red meat: Bacon, all types of sausages, polony and deli meats.	High content of salt, nitrates, haem-iron and saturated fat.
Reduce intake of sugars: Table sugar, honey, sugar sweetened beverages, fruit juices, sweets, desserts and baked goods	Poor nutrient content, contributes to poor glycaemic control, lipid profiles, obesity and inflammation.
If alcohol is consumed it should be in moderation: Wine, spirits, beer etc.	A high intake aggravates glycaemic control, hypertension and triglycerides.

glycaemic control.[11] Low carbohydrate high fat diets require special attention due to their increasing popularity. A recent critical review of 9 meta-analyses was the first review to evaluate actual carbohydrate intake at the final follow up.[13] The results indicated no significant difference in metabolic markers between high and low carbohydrate diets. Very low carbohydrate diets (< 50 g a day) were not adhered to as the mean carbohydrate intake of such diets ranged from 132 – 162 g per day. No study included in this review advocated an increased intake of saturated fats, and thus to recommend such a dietary approach would be inconsistent with the research on low carbohydrate diets.[13]

6.4 Nutritional Quality and Dietary Pattern

Despite the lack of superiority of any dietary approach, the overall quality of the prescribed eating plan needs to be considered (see Table 2). The synergistic effect from a variety of nutrients reduces the risk of developing complications associated with diabetes.[14]

6.5 Nutrient Intake

See Table 3 for a brief overview of the recommendations for specific calorie and nutrient intakes.

6.6 Provision of Healthy Food to South Africans

Emerging research suggests the environment influences dietary intake.[39] In South Africa 64.5% of women considered the cost of food when buying groceries.[40] In contrast, nutritional content and overall health were considered by only 14.1% and 14.3% of women respectively.[40] South Africans consume a diet low in fruit and vegetables and high in fat, sugar and other refined carbohydrates such as mealie meal and both white and brown bread.[40,41] A possible reason for this poor food consumption could be the high perceived-cost of healthy foods and lack of knowledge.[41] Unless healthy food items are made available at an affordable price, education alone is unlikely to succeed in curbing national rates of obesity and type 2 diabetes. Thus, the SEMDSA Guidelines for MNT agree with the South African

Table III: Recommended Nutrient Intakes

Nutrient	Recommendations
Calorie Restriction	• For overweight/ obese adults reducing total energy intake (including carbohydrates, fat, protein and alcohol) is vital to promote weight loss[29] • Calorie requirement should be individualised and calculated by a registered dietitian[29] • A reduction of 350 – 500 kcal from maintenance requirements for patients with a BMI of 30 – 34 kg/m^2 and 500 – 1000 kcal for patients with a BMI ≥40 kg/m^2 in theory should result in a 10% weight loss over 6 months[30] • Very low calorie diets (<800 kcal a day) have shown to be very effective in patients with diabetes, over 8 – 12 weeks under medical supervision[31-34] • To achieve modest weight loss, an intensive lifestyle intervention (MNT, physical activity, behaviour modification with ongoing support is recommended[1]
Macronutrient Distribution	• There is no ideal percentage of calories from carbohydrates, fat or protein[11] • Intake should be individualised based on an assessment of the patient (see Table I) taking in consideration the patient's lifestyle and metabolic goals[1, 12]
Carbohydrates	• Monitoring / regulating carbohydrate intake remains a key strategy for glycaemic control[1] • Carbohydrate intake (both quality and quantity) should be individualised and guided by the patient's glycaemic control[1, 12, 13, 35] • Carbohydrates from whole grains, legumes, low fat milk, vegetables and fruit should be used instead of refined carbohydrates and carbohydrates with added sugar, fats and sodium[1, 28, 36, 37] • Sugars (including fructose powder and high fructose corn syrup) should be ideally < 5 % of total energy intake per day to improve overall health. This equates to the sugar found in commercially products e.g. sauces, without adding additional sugar to the diet[38] • The use of non -nutritive sweeteners (NNS) may reduce overall calorie and carbohydrate intake if substituted for caloric sweeteners. NNS are considered safe if used within the acceptable daily intake levels[1] • Often vitamins, minerals, herbs and spices are marketed as having clinical benefits for people with diabetes. There is however no evidence to support the use of such products and thus should not be included in the MNT[1]
Fats	• The type of fat consumed (saturated fat, monounsaturated fat and polyunsaturated fat) may be more important than total fat intake to prevent CVD[1, 27, 36, 37] • Trans fatty acids should be avoided as far as possible[1,18,25,27] • Replacing saturated fat with either monounsaturated fats or polyunsaturated fats tends to decrease the risk for CVD[36, 37] • Replacing refined carbohydrates with monounsaturated fats or polyunsaturated fats tend to decrease the risk for CVD[36, 37] • Saturated fat and refined carbohydrates tend to have a similar risk for CVD. However, replacing saturated fat with wholegrains tends to lower the risk[36, 37] • A minimum of two servings of fatty fish per week is recommended to ensure an adequate intake of long chain omega 3 fatty acids (EPA and DHA) which reduces risk factors for CVD[1]
Protein	• For individuals with type 2 diabetes with normal renal function, there is no evidence to suggest that the usual recommended protein intake should be modified • For adults with micro and macro albuminuria reducing protein intake to <0.8 g per kg / ideal body weight is not recommended. The former does not alter glycaemia, cardiovascular risk factors or the rate of glomerular filtration (GFR) decline.
Alcohol	• If the patient decides to consume alcohol it should be in moderation (1 drink a day for women and 2 for men)[1] • Alcohol may increase the risk of hypoglycaemia when used in combination with secretagogues and / or insulin. Patients need to be educated on how to consume alcohol safely[1]
Salt	• For general health sodium intake, should be < 2300 mg a day[1] • Further reductions in sodium intake may need to be individualised[1]

National Obesity campaign to create an enabling environment that supports the availability and accessibility to healthy food choices in various settings.

Authors: Hamish van Wyk and Ria Catsicas
Editors: Zaheer Bayat and Aslam Amod

References:

1. American Diabetes Association. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care. 2014;37(1):3821–42. http://care.diabetesjournals.org/content/37/Supplement_1/S120.full.pdf+html Accessed 10 March, 2017
2. Gannon M, Nuttall F. Effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. Diabetes. 2004: 53(9):2375–82. http://diabetes.diabetesjournals.org/content/53/9/2375.full.pdf&sa=U&ei=OzpTU5HpEKO08 QGVuYGwCg&ved=0CDYQFjAF&usg=AFQjCNEBths5zOccm8u81oAO0a02t48mUQ Accessed 10 March, 2017
3. Wing R, Lang W, Wadden T, Safford M, Knowler W, Bertoni A, et al. Benefits of Modest Weight Loss in Improving Cardiovascular Risk Factors in Overweight and Obese Individuals With Type 2 Diabetes. Diabetes Care,2011;34(7):1481–6. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovftm&NEWS=N&AN=00003 458-201107000-00007 Accessed 10 March, 2017
4. van Wyk H. What is the Optimal Lifestyle Modification Advice for Patients with " Pre-diabetes "? South African J Diabetes 2015;(March):32–41. http://reference.sabinet.co.za/document/EJC167493 Accessed 10 March, 2017
5. Mahan KL, Escott-Stump S., Raymond JL. Krause's Food and the Nutrition Care Process. 13th ed. St. Louis, Mo: Elsevier/Saunders; 2012. 253-336 p.
6. Artinian NT, Fletcher GF, Mozaffarian D, Kris-Etherton P, Van Horn L, Lichtenstein AH, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. Circulation 122(4):406–41. http://www.ncbi.nlm.nih.gov/pubmed/20625115 Accessed: 10 March, 2017
7. Lang A, Froelicher ES. Management of overweight and obesity in adults: Behavioral intervention for long-term weight loss and maintenance. Eur J Cardiovasc Nurs. 2006;5(2):102–14. http://www.ncbi.nlm.nih.gov/pubmed/16406709 Accessed 10 March, 2017
8. Costain L, Croker H. Helping individuals to help themselves. Proc Nutr Soc 2005;64(1):89–96. http://www.ncbi.nlm.nih.gov/pubmed/15877927 Accessed 10 March, 2017
9. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. Br J Gen Pract. 2005;55(513):305–12. http://www.ncbi.nlm.nih.gov/pubmed/15826439 Accessed 10 March, 2017
10. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, et al. Weight-Loss Outcomes: A Systematic Review and Meta-Analysis of Weight-Loss Clinical Trials with a Minimum 1-Year Follow-Up. J Am Diet Assoc 2007;107(10):1755–67. http://www.ncbi.nlm.nih.gov/pubmed/17904936 Accessed 10 March, 2017
11. Franz MJ, Powers MA, Leontos C, Holzmeister LA, Kulkarni K, Monk A, et al. The evidence for medical nutrition therapy for type 1 and type 2 diabetes in adults. J Am Diet Assoc. Elsevier Inc.; 2010;110(12):1852–89. http://www.sciencedirect.com/science/article/pii/S0002822310014902 Accessed 10 March, 2017
12. Franz MJ, Boucher JL, Evert AB. Evidence-based diabetes nutrition therapy recommendations are effective: The key is individualization. Diabetes, Metab Syndr Obes Targets Ther 2014;7:65–72. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3938438/ Accessed 10 March, 2017
13. van Wyk HJ, Davis RE, Davies JS. A critical review of low-carbohydrate diets in people with Type 2 diabetes. Diabet Med 2016;33(2):148–57. http://www.ncbi.nlm.nih.gov/pubmed/26413954 Accessed 10 March, 2017
14. Siri-tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fat , carbohydrate , and cardiovascular disease. Am J Clinincal Nutr 2010;(5):502–9. http://ajcn.nutrition.org/content/91/3/502 Accessed 10 March, 2017
15. Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: New insights. Circulation 2011;123(24):2870–91. http://circ.ahajournals.org/content/123/24/2870.full.pdf+html Accessed 10 March, 2017
16. Prior RL. Fruits and vegetables in the prevention of cellular oxidative damage. Am J Clin Nutr . 2003;78(3 SUPPL.):570–8. http://www.ncbi.nlm.nih.gov/pubmed/12936951 Accessed 10 March, 2017
17. Mozaffarian D. Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death. Am J Clin Nutr. 2008;87(6):1991S – 1996S. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L3518726 80\nhttp://nihlibrarysfx.nih.gov:9003/sfx_local?sid=EMBASE&issn=00029165&id=doi:&atitle =Fish+and+n+fatty+acids+for+the+prevention+of+fatal+coronary+heart+disease+and+sudden cardiac death Accessed 10 March, 2017
18. Mozaffarian D, Aro a, Willett WC. Health effects of trans-fatty acids: experimental and observational evidence. Eur J Clin Nutr. Nature Publishing Group; 2009;63 Suppl 2(S2):S5–21. http://dx.doi.org/10.1038/sj.ejcn.1602973 Accessed 10 March, 2017
19. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: A systematic review and meta-analysis. Circulation 2010;121(21):2271–83. http://circ.ahajournals.org/content/121/21/2271.short Accessed 10 March, 2017
20. Mangravite LM, Chiu S, Wojnoonski K, Rawlings RS, Bergeron N, Krauss RM. Changes in Atherogenic Dyslipidemia Induced by Carbohydrate Restriction in Men Are Dependent on Dietary Protein Source. J Nutr. 2011;141(12):2180–5. http://www.ncbi.nlm.nih.gov/pubmed/22031660 Accessed 10 March, 2017
21. Bao W, Li S, Chavarro JE, Tobias DK, Zhu Y, Hu FB, et al. Low Carbohydrate-Diet Scores and Long-term Risk of Type 2 Diabetes Among Women With a History of Gestational Diabetes Mellitus: A Prospective Cohort Study. Diabetes Care. 2016;39(1):43–9. http://care.diabetesjournals.org/content/39/1/43.short Accessed 10 March, 2017
22. Johnson RK, Appel LJ, Brands M, Howard B V., Lefevre M, Lustig RH, et al. Dietary sugars intake and cardiovascular health a scientific statement from the american heart association. Circulation 2009;120(11):1011–20. http://www.ncbi.nlm.nih.gov/pubmed/19704096 Accessed 10 March, 2017
23. Griel AE, Ruder EH, Kris-Etherton PM. The changing roles of dietary carbohydrates: From simple to complex Arteriosclerosis, Thrombosis, and Vascular Biology. 2006. p. 1958–65. http://www.ncbi.nlm.nih.gov/pubmed/16794219 Accessed 10 March, 2017
24. Ryden L, Standl E, Malgorzata B, Van Den Berghe G, Betteridge J, De Boer MJ, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: Executive summary. The task force on diabetes and cardiovascular diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007;28(1):88– 136. http://www.ncbi.nlm.nih.gov/pubmed/17220161 Accessed 10 March, 2017
25. Robert H Eckel MDF, John M Jakicic P, Jamy D Ard MD, Nancy Houston Miller RNBSNF, Van S Hubbard MDP, Cathy A Nonas MSRD, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk. J Am Coll Cardiol. 2013;63(25):1–46. http://dx.doi.org/10.1016/j.jacc.2013.11.003\npapers3://publication/doi/10.1016/j.jacc.201 3.11.003 Accessed 10 March, 2017
26. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association. Circulation 2011;123(20):2292–333. http://circ.ahajournals.org/content/123/20/2292.full.pdf Accessed 10 March, 2017
27. Vannice G, Rasmussen H. Position of the academy of nutrition and dietetics: Dietary fatty acids for healthy adults. J Acad Nutr Diet. 2014;114(1):136–53. http://www.ncbi.nlm.nih.gov/pubmed/24342605 Accessed 10 March, 2017
28. Jenkins DJ et al. Effect of legumes as part of a low glycaemic index diet on glycaemic control and cardiovascular risk factors in type 2 diabetes mellitus: a randomized controlled trial. Arch Intern Med 2012;172(21):1653–60. http://www.ncbi.nlm.nih.gov/pubmed/23089999 Accessed 10 March, 2017
29. Seagle HM, Strain GW, Makris A, Reeves RS. Position of the American Dietetic Association: weight management. J Am Diet Assoc 2009;109:330–46. http://www.ncbi.nlm.nih.gov/pubmed/19244669 Accessed 10 March, 2017
30. Astrup A. Treatment of Obesity. In: DeFronzo RA, Ferrannini E, Keen H, Zimmet P, editors. International Textbook of Diabetes Mellitus Third Edit. 2004. p. 673–90. http://www.irf.dk/download/pdf/hypertension/treatment_of_obesity.pdf Accessed 10 March, 2017
31. Hammer S, Snel M, Lamb HJ, Jazet IM, van der Meer RW, Pijl H, et al. Prolonged Caloric Restriction in Obese Patients With Type 2 Diabetes Mellitus Decreases Myocardial Triglyceride Content and Improves Myocardial Function. J Am Coll Cardiol. 2008;52(12):1006–12. http://www.ncbi.nlm.nih.gov/pubmed/18786482
32. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: Normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011;54(10):2506–14. http://www.ncbi.nlm.nih.gov/pubmed/21656330 Accessed 10 March, 2017
33. Parretti HM, Jebb SA, Johns DJ, Lewis AL, Christian-Brown AM, Aveyard P. Clinical effectiveness of very-low-energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials. Obes Rev.

2016;17(3):225–34. http://doi.wiley.com/10.1111/obr.12366 Accessed 10 March, 2017

34. Steven S, Taylor R. Restoring normoglycaemia by use of a very low calorie diet in long- and short-duration Type 2 diabetes. Diabet Med 2015;32:1149–55. http://doi.wiley.com/10.1111/dme.12722 Accessed 10 March, 2017
35. Sheard NF, Clark NG, Brand-Miller JC, Franz MJ, Pi-Sunyer XF, Mayer-Davis E, et al. Dietary Carbohydrate (Amount and Type) in the Prevention and Management of Diabetes. Diabetes Care . 2004;27(9):2266–71. http://www.ncbi.nlm.nih.gov/pubmed/15333500 Accessed 10 March, 2017
36. Jakobsen MU, Dethlefsen C, Joensen AM, Stegger J, Tjønneland A, Schmidt EB, et al. Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: Importance of the glycaemic index1-3. Am J Clin Nutr 2010;91(6):1764–8. http://www.ncbi.nlm.nih.gov/pubmed/20375186 Accessed 10 March, 2017
37. Li Y, Hruby A, Bernstein AM, Ley SH, Wang DD, Chiuve SE, et al. Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease. J Am Coll Cardiol 2015;66(14):1538–48. http://linkinghub.elsevier.com/retrieve/pii/S0735109715046914 Accessed 10 March, 2017
38. World Health Organization. Guideline : Sugars intake for adults and children. 2015;(March):1– 48. http://apps.who.int/iris/bitstream/10665/149782/1/9789241549028_eng.pdf Accessed 10 March, 2017
39. Bray GA, Bouchard C. Handbook Of Obesity: Epidemiology, Etiology, and Physiopathology. 3rd ed. Florida: CDC Press; 2014. 413 - 457 p.
40. Shisana o, Labadarios D, Rehle T, Simbayi L, Zuma K, Dhansay A, Reddy P, Parker W, Hoosain E, Naidoo P, Hogoro C, Mchiza Z, Steyn NP, Dwane N, Makoae M, Maluleke T, Ramlagan S, zungu N, Evans MG, Jacobs L FM& S-1 T. The South African National health and Nutrition Examination Survey SANHANES-1 2013. 1-78 p. http://www.hsrc.ac.za/uploads/pageNews/72/SANHANES-launch edition (online version).pdf Accessed 10 March, 2017
41. South African Department of Health. Strategy For the Prevention and Control of Obesity in South Africa 2015-2020. 2015;1. http://www.health-e.org.za/wp-content/uploads/2015/12/National-Strategy-for-prevention-and-Control-of-Obesity-4-August-latest.pdf Accessed 10 March, 2017

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 7: Physical activity and type 2 diabetes

SEMDSA Type 2 Diabetes Guideline Expert Committee

SEMDSA 2017 Recommendations	
Optimising physical activity is an integral part of the management of type 2 diabetes.	C
Physical activity lowers morbidity and mortality in type 2 diabetes.	B
Both aerobic and resistance exercise confer benefit in type 2 diabetes.	B
All people with type 2 diabetes should be encouraged to perform 150 minutes of aerobic exercise, at 50 to 70% of maximal heart rate, per week, as well as resistance training three (3) times per week.	B
Flexibility and balance training are recommended 2–3 times per week for older adults with diabetes.	B
Co-morbidities and cardiovascular risk need careful assessment before advising on a physical exercise regimen.	C
Patients using insulin and/or sulphonylureas should be counselled about the symptoms and risks of hypoglycaemia before starting with a physical exercise regimen.	B

7.1 Introduction

Randomised controlled trials have demonstrated that physical activity can delay the progression of impaired glucose tolerance to type 2 diabetes, when combined with dietary changes.[1] In patients with type 2 diabetes, regular physical activity significantly improves glycaemic control, reduces cardiovascular risk factors and may reduce chronic medication dosages.[2] Regular physical activity may also improve symptoms of depression and improve health-related quality of life. These guidelines are adapted from the Canadian and American Diabetes Association's guidelines.

7.2 Benefits of regular physical activity

Moderate to high levels of physical activity and cardiorespiratory fitness are associated with substantial reductions in morbidity and mortality in both type 1[3] and type 2 diabetes mellitus.[4] Large cohort studies have demonstrated that, in people with type 2 diabetes, regular physical activity and moderate to high levels of cardiorespiratory fitness are associated with reductions in cardiovascular and overall mortality of 39-70% over a 15 to 20 year period.[5-7]

People with type 2 diabetes will derive the following benefits from regular physical activity:[8-10]

- Increased cardiorespiratory fitness
- Improved glycaemic control
- Decreased insulin resistance
- Improved blood lipid profile
- Improved blood pressure
- Maintenance of weight loss
- Reduced abdominal and overall fat percentage
- Improved well-being
- Decreased stress and anxiety
- Improved mobility in overweight people

7.3 Physical activity recommendations for people with type 2 diabetes.

People with type 2 diabetes should be advised to perform at least 150 minutes per week of moderate-intensity aerobic physical activity, with the aim of achieving and maintaining a heart rate that is 50-70% of the maximum heart rate. In the absence of contraindications, people with type 2 diabetes should also be encouraged to perform resistance training three times per week.[11] Table I and II summarises these recommendations. The maximum heart rate is calculated by subtracting the chronologic age from 220.[12]

7.3.1 Exercise Prescription Details

Both aerobic and resistance exercise are recommended for most people with diabetes (Tables I and II). Walking is often the most popular and most feasible type of aerobic exercise in overweight, middle-aged, and elderly people with diabetes. For those who struggle with pain upon walking (e.g. due to osteoarthritis), semi-recumbent cycling may provide an alternative. For most middle-aged individuals, moderately brisk walking on level ground or semi-recumbent cycling would be an example of moderate aerobic exercise, while brisk walking up an incline or jogging would be vigorous aerobic exercise.

Resistance exercise performed 2 or 3 times per week may provide benefits that complement those of aerobic training (e.g. increased strength and vigour, reduced body fat, increased resting metabolic rate).[13,14,15] The studies reporting the greatest impact of resistance exercise on HbA_{1C} had subjects progress to 3 sets (with approximately 8 repetitions per set) of resistance-type exercises at moderate to high intensity (i.e. the maximum weight that can be lifted 8 times while maintaining proper form), three (3) times per week[16,17] or more.[18,19] However, significant

Table I: Aerobic exercise recommended for individuals with type 2 diabetes[23]

Definition	Intensity	Frequency	Examples
Activities that consist of rhythmic, repetitive and continuous movement of the same large muscle groups for at least 10 minutes at a time	Moderate: 50-70% of maximum heart rate	Minimum 150 minutes per week	Cycling, brisk walking, continuous swimming, dancing, water aerobics, raking leaves
	Or		
	Vigorous: > 70% of maximum heart rate	Minimum 75 minutes per week	Brisk walking up an incline, jogging, aerobics, hockey, basketball, fast swimming, fast dancing
	Or		
	Equivalent combination of moderate and vigorous aerobic exercise		

Table II: Resistance exercise recommended for individuals with type 2 diabetes[23]

Definition	Recommended Frequency	Examples
Activities of brief duration involving the use of weights, weight machines or resistance bands to increase muscle strength and endurance.	Two to three times per week: • Start with one set using a weight which you can perform 15-20 repetitions while maintaining proper form. • Progress to two sets and decrease the number of repetitions to 10-15 while increasing the weight slightly. If you cannot complete the required repetitions while maintaining proper form reduce the weight. • Progress to three sets of 8 repetitions performed using an increased weight, ensuring proper form is maintained.	Exercise with weight machines. Free weight lifting. Thera-Band® exercises.

[a] Resistance exercise should only be attempted if there are no contraindications to this kind of activity

reductions in HbA_{1C} and body fat have been achieved with twice-weekly resistance exercise in combination with regular aerobic exercise.[10,20] The effects of resistance exercise and aerobic exercise on glycaemic control are additive.[21]

Individuals who wish to begin resistance exercise should receive initial instruction and periodic supervision by a qualified exercise specialist where possible, to maximise benefits while minimising risk of injury. A meta-analysis of trials evaluating resistance exercise with less supervision reported less beneficial impact on glycaemic control, insulin resistance and body composition than studies with greater supervision.[14] Individuals with diabetes should be encouraged to increase the amount of activities of daily living, such as housework, gardening and walking around shopping centres and the office at regular intervals. All people with diabetes, should be encouraged to reduce sedentary time, particularly by breaking up extended amounts of time (>90 mins) spent sitting.[22]

7.4 Minimising the risk of exercise related adverse events

7.4.1 General

Patients with multiple cardiovascular risk factors, should be assessed before an exercise programme is recommended.[8] Certain conditions might be contraindications to specific types of exercise, or predispose to injury:

- Uncontrolled hypertension
- Severe autonomic neuropathy
- Severe peripheral neuropathy or history of foot ulcers
- Unstable proliferative retinopathy
- Orthopaedic injuries.

The patient's age and previous physical activity level should also be taken into account.

In general ECG stress testing may be indicated for individuals matching one or more of these criteria:[24]

Age > 40 years , with or without CVD risk factors other than diabetes

Age > 30 years and Type 2 diabetes of >10 years duration

Hypertension

Cigarette smoking

Dyslipidaemia

Proliferative or pre-proliferative retinopathy

Nephropathy, including microalbuminuria

Any of the following, regardless of age

Known or suspected coronary artery disease (CAD, cerebrovascular disease, and/or peripheral arterial disease)

Autonomic neuropathy

Advanced nephropathy with renal failure.

7.4.2 Exercise in the Presence of Specific long-term complications:

Diabetic Retinopathy

In the presence of proliferative diabetic retinopathy (PDR) or severe non-PDR (NPDR), vigorous aerobic or resistance exercise

may be contraindicated because of the risk of triggering vitreous haemorrhage or retinal detachment.[25] These include jumping, jarring and head-down activities.[11]

Peripheral Neuropathy

Decreased pain sensation and a higher pain threshold in the extremities result in increased risk of skin breakdown and infection and of Charcot joint destruction with some forms of exercise. However, studies have shown that moderate-intensity walking may not lead to increased risk of foot ulcers or re-ulceration in those with peripheral neuropathy.[26] In addition, 150 min/week of moderate exercise was reported to improve outcomes in patients with milder forms of neuropathy.[27] All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. Anyone with a foot injury or open wound should be restricted to non–weight-bearing activities.

Autonomic Neuropathy

Autonomic neuropathy can increase the risk of exercise-induced injury or adverse event through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and higher susceptibility to hypoglycaemia.[28] Cardiovascular autonomic neuropathy (CAN) is also an independent risk factor for cardiovascular death and silent myocardial ischemia.[29] Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Albuminuria and Nephropathy

Physical activity can acutely increase urinary protein excretion. However, there is no evidence that vigorous exercise increases the rate of progression of diabetic kidney disease. Furthermore, there is no need for any specific exercise restrictions for people with diabetic kidney disease, unless there are other complications.[30]

7.4.4 Hypoglycaemia

In individuals taking insulin and/or insulin secretagogues, physical activity can cause hypoglycaemia if the medication dose is not reduced or carbohydrate consumption is not increased.[8] In these individuals, if pre-exercise blood glucose levels are below 5.5 mmol/L, approximately 15-30 g carbohydrate should be ingested before exercise. (The actual amount will be dependent on injected insulin dose, exercise duration and intensity, and results of blood glucose monitoring).[23]

In individuals whose diabetes is controlled by lifestyle or oral hypoglycaemic agents that do not increase insulin levels, the risk of developing hypoglycaemia during exercise is minimal, and most individuals will not need to monitor their blood glucose levels or be required to supplement with carbohydrate for exercise lasting < 1 hour.[23]

7.5 Physical activity counselling and motivation

Studies have found that structured physical activity counselling by a physician[36], skilled healthcare personnel or case managers[31,32] increased physical activity levels, improved glycaemic control[33], reduced the need for oral anti-hyperglycaemic agents and insulin, and produced modest but sustained weight loss.[33] Patients should be encouraged to set specific physical activity goals, anticipate likely barriers to physical activity (e.g. weather, competing time commitments) and develop strategies to overcome these barriers.[34] Having patients record their daily physical activity has been shown to increase physical activity levels and improve self-efficacy (confidence in one's own ability to successfully carry out a behaviour).[35] Self-efficacy is a very strong cognitive predictor of both aerobic and resistance exercise participation in people with diabetes.[35] However, the impact of physical activity counselling on glycaemic control, fitness, body composition and lipids is not as significant as that achieved through a supervised aerobic and resistance exercise programme.[36] Having social support (e.g. exercising with a friend or partner) facilitates and aids in motivating regular physical activity.[37]

Author: Andrew Heilbrunn
Editors: Aslam Amod and Fraser J Pirie

References

1. Knowler WC, Fowler SE, Hamman RF et al,10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374(9702)1677-1686.
2. Thomas D, Elliot EJ, Naughton GA. Exercise for Type 2 diabetes. Cochrane Database of Systematic Reviews 2006, Issue 3 Art. No.: CD002968. Doi: 10.1002/14651858.CD002968.pub 2.
3. Moy CS, Songer TJ, La Porte RE, et al. Insulin-dependent diabetes mellitus, physical activity, and death. Am J Epidemiol 1993; 137:74-81.
4. Sigal RJ, Kenny G, Oh P, et al. Physical activity and diabetes. Canadian Diabetes Association clinical practice guidelines expert committee. Can J Diabetes. 2008; 32(Suppl. 37): S37-S39.
5. Hu G, Jousilahti P, Barengo NC, et al. Physical activity, cardiovascular risk factors, and mortality among Finnish adults with diabetes. Diabetes Care. 2005; 28:799-805.
6. Hu FB, Stampfer MJ, Solomon C, et al. Physical activity and risk for cardiovascular events in diabetic women. Ann Intern Med.2001; 134:96-105.
7. Gregg EW, Gerzoff RB, Caspersen CJ, et al. Relationship of walking to mortality among US adults with diabetes. Arch Intern Med. 2003; 163:1440-1447.
8. Standards of medical care in diabetes. ADA position statement. Diabetes Care. 2011; 34 (Suppl1): S24-S25.
9. Umpierre D, Ribeiro AB, Kramer CK et al. Physical Activity advice only or structured exercise training and association with HbA_{1c} levels in type 2 diabetes. A systematic review and meta-analysis. JAMA 2011305,(17): 1790-1799.
10. Balducci D, Zanuso S, Nicolucci A, et al. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). Arch Intern Med. 2010; 170: 1794-1803.
11. Albright A, Franz M, Hornsby G, et al. American College of Sports Medicine. Position Stand: exercise and type 2 diabetes. Med Sci Sports Exerc 2000; 32(7):1345-60.
12. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate. JACC 2001; 37, (1): 153-156.
13. Snowling NJ and Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis Diabetes Care. 2006; 29: 2518- 2527
14. Gordon BA, Benson AC, Bird SR, Fraser SR. Resistance training improves metabolic health in type 2 diabetes: a systematic review. Diabetes Res Clin Pract. 2009; 83: 157-175
15. Eves ND and Plotnikoff RC. Resistance training and type 2 diabetes. Considerations for implementation at the population level. Diabetes Care. 2006; 29: 1933-1941

16. Castaneda C, Layne JE, Munoz-Orians L. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care. 2002; 25: 2335-2341
17. Dunstan DW, Daly RM, Owen N. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. Diabetes Care 2002; 25: 1729- 1736
18. Durak EP, Jovanovic-Peterson L, Peterson CM. Randomized crossover study of effect of resistance training on glycemic control, muscular strength, and cholesterol in type 1 diabetic men. Diabetes Care 1990; 13: 1039-1043.
19. Cauza E, Hanusch-Enserer U, Strasser B. The relative benefits of endurance and strength training on the metabolic factors and muscle function of people with type 2 diabetes mellitus. Arch Phys Med Rehabil. 2005; 86: 1527-1533.
20. Church TS, Blair SN, Cocreham S. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial JAMA 2010; 304: 2253- 2262.
21. Sigal RJ, Kenny GP, Boule NG. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med. 2007;147: 357-369.
22. Katzmarzyk PT, Church TS, Craig CL,Bouchard C. Sitting time and mortality from allcauses, cardiovascular disease, and cancer. Med Sci Sports Exerc 2009;41:998–1005
23. Sigal RJ, Amstrong MJ, et al. Physical Activity and Diabetes. Canadian Diabetes Association clinical practice guidelines expert committee. Can J Diabetes. 2013; (Suppl. 37): S40-S44.
24. Colberg SR, Sigal RJ, Fernhall B. Exercise and Type 2 Diabetes. Diabetes Care 2010;33(12):147-167.
25. Aiello LP, Wong J, Cavallerano J, Bursell SE, Aiello LM. Retinopathy. In Handbook of Exercise in Diabetes. 2nd ed Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002: p 401–413
26. Lemaster JW, Reiber GE, Smith DG, Heagerty PJ, Wallace C. Daily weight bearing activity does not increase the risk of diabetic foot ulcers. Med Sci Sports Exerc 2003; 35:1093–1099.
27. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care 2006; 29:1294–1299.
28. Spallone V, Ziegler D, Freeman R, et al. Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 2011; 27:639–653.
29. Pop-Busui R, Evans GW, Gerstein HC, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010; 33:1578–1584.
30. Mogensen CE. Nephropathy. In Handbook of Exercise in Diabetes. 2nd ed. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, VA, American Diabetes Association. 2002: 433–449
31. Kirk A, Mutrie N, MacIntyre P, Fisher M. Effects of a 12-month physical activity counseling intervention on glycaemic control and on the status of cardiovascular risk factors in people with Type 2 diabetes. Diabetologia. 2004; 47: 821- 832.
32. Wolf AM, Conaway MR, Crowther JQ. Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving Control with Activity and Nutrition (ICAN) study Diabetes Care 2004; 27: 1570-1576.
33. Norris SL, Zhang X, Avenell A. Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. Cochrane Database Syst Rev 2. 2005 CD004095
34. DeWalt DA, Davis TC, Wallace AS. Goal setting in diabetes self-management: taking the baby steps to success Patient Educ Couns 2009; 77: 218- 223.
35. Plotnikoff RC, Trinh L, Courneya KS. Predictors of physical activity in adults with type 2 diabetes. Am J Health Behav 2011; 35: 359- 370.
36. Petrella RJ, Koval JJ, Cunningham DA, Paterson DH. Can primary care doctors prescribe exercise to improve fitness? The step test exercise prescription (STEP) project. Am J Prev Med 2003; 24: 316- 322.
37. van Dam HA, van der Horst FG, Knoops L. Social support in diabetes: a systematic review of controlled intervention studies Patient Educ Couns 2005; 59: 1- 12.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 8: Glycaemic Targets

SEMDSA 2017 Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Involve the patient with type 2 diabetes in the discussion about setting glycaemic goals, taking into account the duration of their diabetes, general health status, life expectancy and risk of hypoglycaemia.	C
Aim to achieve and maintain a target HbA1c ≤ 7% in most patients, to prevent microvascular disease.	A
Achieving an HbA1c target ≤ 7 earlier in the course of type 2 diabetes will also reduce macrovascular disease and mortality.	B
In newly diagnosed patients in good general health the target HbA1c should be <6.5% to prevent further retinopathy and nephropathy, provided it can be achieved safely.	A
A target HbA1c of 7.1 to 8.5% may be acceptable for the elderly, the frail, those with limited life expectancy, multiple co-morbidities, severe vascular disease, advanced chronic kidney disease, recurrent severe hypoglycaemia, or hypoglycaemic unawareness.	B
Monitor the HbA1c at least every 6 months in patients with stable glycaemic control who are maintaining their target, and at 3 month intervals in patients who are not at target in whom interventions have intensified.	C
Self-monitoring of blood glucose (SMBG) should be encouraged but optimal use requires regular review and interpretation by both the patient and health care provider.	C
SMBG targets should be individualised to achieve the appropriate HbA1c target. For individuals with an HbA1c target of ≤ 7%, the recommended fasting/preprandial SMBG target is 4.0 to 7.0 mmol/L and the post-prandial SMBG targets is 5.0 to 10 mmol/L. These targets can be adjusted based on the individual's response.	C
Patients using insulin 2-4 times a day should perform SMBG at least 3 times a day.	B
Patients on basal insulin must perform SMBG at least once a day (fasting glucose), in order to titrate their doses. More frequent testing may be needed to monitor for post-prandial hyperglycaemia.	B
For individuals on oral agents, SMBG should be initiated as part of an overall education process but for most patients 3-5 tests a week is all that may be required.	C
More intensive testing is necessary in certain situations, such as acute illness, periods of poor glycaemic control, fasting, frequent hypoglycaemia and pregnancy.	C

Introduction

The primary purpose of treating glycaemia in patients with type 2 diabetes mellitus is to reduce blood glucose sufficiently to relieve any symptoms of hyperglycaemia, but mostly to prevent or delay the onset of microvascular and macrovascular complications (when treatment is started early in the course of the disease). To achieve these goals, targets need to be set for both short and long term glucose control. This will prevent the tendency to under treat patients. This section outlines appropriate targets for long-term glycaemic control as assessed by glycated haemoglobin A_{1C} (HbA1c), and the appropriate blood glucose levels needed to attain those targets. Refer to Chapter 3 for a discussion on HbA1c measurement.

HbA1c targets

Understanding the need for individualised HbA1c targets

Type 2 diabetes is diagnosed on the basis of elevated blood glucose and HbA1c levels that predict a significantly increased risk of microvascular disease;[1] by the time the HbA1c exceeds 7.5%, the risk of microvascular disease is increased 2.5-5 fold.[2,3] Type 2 diabetes is also a strong risk factor (2-4 fold increased risk) for cardiovascular disease,[4–6] although this risk is present even in the prediabetes stage.[7] The incidence of both microvascular and cardiovascular disease rises with the degree of hyperglycaemia,[1] making it a reasonable hypothesis that lowering blood glucose will reduce complications.

Randomised controlled trials of intensive versus non-intensive glycaemic control have provided convincing evidence for microvascular disease risk reduction. The Kumamoto,[8] United Kingdom Prospective Diabetes Study (UKPDS),[9] Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE),[10] Action to Control Cardiovascular Risk in Diabetes (ACCORD)[11] and Veterans Affairs Diabetes Trial (VADT)[12] achieved HbA1c levels between 6.4% and 7.1% and all demonstrated microvascular benefits.

The relationship between intensive glucose control and cardiovascular disease is not as clear. In the UKPDS, early intensive glycaemic control reduced cardiovascular events and mortality in recently diagnosed individuals over 10 years of treatment, but the reduction was only statistically significant after a further 10 years of observation, even though patients were no longer intensively controlled.[13,14]

Further observational analysis of the UKPDS confirmed that every 1% reduction of HbA1c was associated with reductions in risk of 21% for any end point related to diabetes, 21% for deaths related to diabetes, 14% for myocardial infarction, and 37% for microvascular complications. No threshold of risk was observed for any end point, and the lowest risk of complications was predicted to occur at an HbA1c of 6.0%. Yet these expected cardiovascular and mortality benefits were not evident in ACCORD, ADVANCE and VADT.[12,15,16]10,251 patients (mean age, 62.2 years In fact, the ACCORD study was stopped prematurely because of an unexplained increase in mortality.

These trials have been reviewed and analysed extensively to try to understand their lack of cardiovascular and mortality benefit.[17–19] What is known is that they included older individuals (mean age > 60 yrs) with long diabetes duration (8.5 to 10 yrs); more than a third already had established cardiovascular disease; non-glycaemic risk factors such as blood pressure and dyslipidaemia were better treated than in previous cardiovascular outcomes trials; and the total number of vascular events was lower than expected. Further sub-group and post-hoc analysis of these trials show that patients with shorter diabetes duration, better glycaemic control and no / lesser degrees of cardiovascular disease at baseline benefitted more from the intensive intervention.[20–22] All three studies reported higher rates of severe hypoglycaemia in the intensively treated group. Severe hypoglycaemia was a strong risk factor for cardiovascular events and mortality, but more so in the cohorts that were not treated intensively.[23,24]

Longer-term follow-up (up to ten years post-trial) in UKPDS showed significant reductions cardiovascular events and mortality despite the loss of intensive glycaemic control; ADVANCE remained neutral for cardiovascular events and mortality[25] but lowered the rate of end-stage renal disease;[26] the VADT cohort showed a reduction in the risk of cardiovascular events;[27] and ACCORD had a neutral effect for cardiovascular events and no further increase in mortality.[28]

An interpretation summary after a review of the current evidence would be as follows:

1. Intensive glycaemic control significantly reduces microvascular outcomes (especially diabetic kidney disease and retinopathy), even in older individuals and those with diabetes of longer duration, with clinical trial evidence of benefit at HbA1c levels as low as 6.4%, and observational trial benefits at HbA1c levels as low as 6.0%.[8,9,11,12,16,29]
2. Intensive glycaemic control earlier in the course of diabetes appears to have a "legacy effect" whereby an earlier period of intensive control results in better outcomes many years later, even after glycaemic control may have deteriorated.[13,14,27]
3. Long-term macrovascular and mortality benefits are more likely to accrue when intensive glycaemic control is achieved earlier in the course of diabetes and in the absence of established cardiovascular disease,[9,13] rather than later.[12,15,16]
4. Severe hypoglycaemia is a strong risk factor for cardiovascular events and mortality in patients fitting the profile of the ACCORD, ADVANCE and VADT cohort (age 60+ yrs; diabetes duration > 8yrs; high prevalence of cardiovascular disease or risk factors).[12,15,16] Despite numerous analyses, causality between severe hypoglycaemia and outcomes has not been proven.[17,23,24,30,31] It is equally possible that severe hypoglycaemia may be a marker of patient vulnerability i.e. that patients who are ill and at risk for mortality, are more likely to develop severe hypoglycaemia.16 Nevertheless, it remains a risk factor for cardiovascular events and mortality and must be avoided.
5. Targeting intensive glycaemic control (HbA1c <6.5%) in individuals with longer duration of diabetes (> 8 years) or those with very high cardiovascular risk, does not improve cardiovascular or mortality outcomes,[16] and may be harmful when done aggressively.[15] In these patients with advanced disease, the aim should be to achieve the lowest HbA1c reasonably possible to prevent microvascular disease, without causing hypoglycaemia.[17]
6. Optimal treatment of non-glucose risk factors, such as smoking, dyslipidaemia, hypertension and pre-existing cardiac or vascular disease probably led to an overall reduction in the expected number of vascular events in the trials discussed above.[17] These risk factors are often present before the diagnosis of diabetes, which is when cardiovascular risk increases. They should be sought early and managed aggressively. A multifactorial intervention does best at improving patient outcomes.[32]

Choosing individualised HbA1c Targets

The discussion above provides the basis for individualised goals of treatment and HbA1c targets.

- For the majority of patients, the recommended HbA1c target is <7 % to prevent microvascular complications, and macrovascular complications when intensive treatment is instituted early in the course of the disease.[13]
- For newly diagnosed patients in good general health and reasonable life expectancy an HbA1c target of <6.5 % is reasonable to aim for to further reduce microvascular risk, provided it can be achieved safely.[16,11,22,29] As a guide, reasonable life expectancy may be defined as being longer than the time taken to achieve benefit in clinical trials, which for UKPDS-33 was 10 years.[9]

Figure I: Selection of HbA1c Targets according to risk (adapted from Ismail-Beigi et al[33])

Patient features	< 6.5 %	< 7 %	7 - 8 %
Risks of hypoglycaemia / drug interactions	Low	⟷	High
Disease duration	Newly diagnosed	⟷	Long Standing
Life expectancy	Long	⟷	Short
Major comorbidities	Absent	⟷	Severe
Established macrovascular disease	Absent	⟷	Severe
Patient attitude	Highly motivated Adherent Good self-care capacity	⟷	Not motivated Non-adherent Poor self-care capability
Resources and support	Readily available	⟷	Limited

- For those who are frail, have a high level of dependency, multiple comorbidities, severe cardiac or vascular disease, advanced renal disease, limited life expectancy or hypoglycaemic unawareness, an HbA1c target between 7.1% and 8.5% may be reasonable. For palliative care, for example, the aim would be simply to avoid symptomatic hyperglycaemia.

Figure I illustrates some of the factors that need to be considered when discussing individualised HbA1c targets with the patient.

Blood Glucose Targets

Fasting plasma glucose (FPG) ≤6.0 mmol/l is generally classified as "normal" using the WHO criteria. While a meta-analysis of 38 prospective studies has found an association of increased risk of CV events with a FPG >5.5 mmol/l[34], the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) Study suggested a FPG below 7.0 mmol/l is low-risk for CVD[35]. Overall, a fasting or pre-prandial (before a meal) target of 4.0-7.0 mmol/l is recommended.[36] In non-diabetic individuals, the peak post-prandial Glucose (PPG) generally does not exceed 7.8 mmol/l. However, the DECODE Study has demonstrated a linear progression between the post-glucose load glucose level and CVD with no 'lower' limit cut-off.[12] The International Diabetes Federation (IDF) recommends a PPG target of <9.0 mmol/l,[37] while the American Diabetes Association (ADA) recommends a PPG target of ≤10 mmol/l.[38] The actual target to be aimed for will depend on the target HbA1c (see Table I).

Monitoring glycaemic control using HbA1c

HbA1c reflects average levels of glycaemia over 2-3 months and should be performed routinely in all patients with diabetes, both at the initial appointment and then regularly as part of continuing care, to aid in therapeutic decisions. The frequency of HbA1c testing is dependent upon the clinical situation and response to therapy, but should not be done less than every 6 months.

Table I: Average Fasting and Post-prandial glucose levels in relation to HbA1c

Target HbA1c	Target FPG	Target PPG
< 6.5 %	4.0-7.0 mmol/l	< 8 mmol/l
< 7 %	4.0-7.0 mmol/l	< 10 mmol/l
< 8 %	4.0-7.0 mmol/l	< 12 mmol/l

Recommendations:

- HbA1c should be checked every 6 months in patients with stable control who are meeting their target goal
- HbA1c should be checked at 3 month intervals in patients who are not reaching their target goal and in whom therapy has been changed or intensified.
- Point-of-care testing can be used for monitoring (but not diagnosis), provided that assay and measurement standards are met (Refer to Chapter 3).

Understanding HbA1c and average glucose

The level of HbA1c at any point in time is contributed to by all circulating erythrocytes, from the oldest (120 days) to the youngest. HbA1c is a "weighted" average of blood glucose levels during the preceding 120 days of the erythrocytes' life span, meaning that glucose levels in the preceding 30 days contribute substantially more to the level of HbA1c than do glucose levels from 90-120 days earlier. This explains why the level of HbA1c can increase or decrease relatively quickly with large changes in glucose; it does not take 120 days to detect a clinically meaningful change in HbA1c following a clinically significant change in average glucose.

The HbA1c assay is now a well-standardised test and a useful tool for guiding therapy and predicting outcomes. However, its interpretation is not intuitive, as practitioners and patients are more familiar with discussing glucose levels rather than a percentage test. Understanding the relationship between HbA1c and average glucose can be useful in educating patients and adjusting therapy. The correlation between HbA1c and average glucose is strong enough to justify reporting both the HbA1c result and an estimated average glucose (eAG) result when a clinician orders the HbA1c test. Laboratories are now encouraged to report both values.

Table II shows the correlation of various levels of HbA1c with the corresponding eAG values (A calculator for converting HbA1c results into eAG is available at http://professional.diabetes.org/GlucoseCalculator.aspx).

Table II: Estimated average glucose levels in relation to HbA_{1c} (from: Nathan DM et al[39])

HbA_{1c} (%)	eAG (mmol/l)
6	7.0
7	8.6
8	10.2
9	11.8
10	13.4
11	14.9
12	16.5

Limitations of HbA_{1c}

The HbA_{1c} is dependent upon the lifespan and turnover time of the red blood cells. In situations of altered red blood cell turnover time (such as anaemia's, blood loss, renal failure etc.) and when haemoglobinopathies are present, the HbA_{1c} may not be a true reflection of prevailing levels of glycaemia. When the HbA_{1c} is discrepant with the results of self-monitoring of blood glucose (SMBG), the clinician should consider the above possibilities and request laboratory screening for a possible haemoglobinopathy. The HbA_{1c} also does not measure the frequency or severity of hypoglycaemia or glycaemic variability and thus results must be interpreted together with SMBG records and the patient history.

Monitoring of glycaemic control using SMBG

SMBG for individuals on insulin

SMBG is an essential and integral part of effective therapy and will help drive treatment decisions and insulin dose adjustments. However, optimal use of SMBG requires regular review and interpretation by both the patient and doctor or diabetes nurse educator. The frequency depends on the insulin regimen being used:

- In those individuals injecting insulin two to four times per day, testing should be undertaken at least three times per day.[40,41]
- In those individuals on once-daily insulin, with or without oral hypoglycaemic agents, there is insufficient evidence regarding when or how often to prescribe SMBG. However, it is generally recommended that once-daily testing, first thing in the morning, should be done to assess the efficacy of the basal insulin dose.
- Should the HbA_{1c} be above target in the face of a satisfactory fasting glucose, a second test should be performed after the largest meal of the day to exclude postprandial hyperglycaemia. However, it is considered unnecessary to perform a postprandial test if the HbA_{1c} is at target.[42]

SMBG for individuals on oral glucose lowering drugs

Evidence is conflicting, and there are numerous publications discussing the advantages and disadvantages of SMBG in patients being treated with oral hypoglycaemic agents. [43-45] However, in those who were recently diagnosed, SMBG[46] and structured testing combined with appropriate patient education has been shown to be of benefit.[47-50] A meta-analysis of appropriate studies has suggested that in patients on oral agents, the HbA_{1c} may be reduced by 0.25 % at 6 months. Performing SMBG alone without appropriate education does not reduce blood glucose levels without concurrent education.

The IDF (2009)[42] recommends that SMBG should only be used in patients who have been taught the skills to incorporate SMBG into their diabetes care plan. It should be considered at the time of diagnosis to enhance understanding, and ongoing SMBG may assist patients in understanding and participating in their care. However, SMBG protocols should be individualised and the purpose of using SMBG should be agreed upon by the patient and the healthcare provider.

SMBG Recommendations

- SMBG should only be initiated in patients on oral agents only, when prescribed as part of an overall educational process (C)
- For most patients, 3-5 tests per week (<25 strips per month) is all that may be required (C)
- Testing must be structured and meaningful
- Patients need to understand their (glycaemic) targets and know what to do if these are not being achieved.

Circumstances demanding more frequent SMBG

In certain situations it may be necessary to advocate more regular testing which may be up to 4 times a day or more. These include:

- Acute illness
- Periods of poor glycaemic control
- Frequent hypoglycaemic episodes
- Pregnancy
- Adjustments to therapy.

Continuous glucose monitoring

Continuous Glucose Monitoring (CGM) may be done either to assess retrospective glycaemic control to aid in therapeutic decisions or to assess the results of changes in therapy. This is seldom employed in patients with type 2 diabetes. Longer term CGM is primarily employed in unstable type 1 patients to allow patients real time monitoring of glucose profiles. It may be useful in insulin-treated type 2 diabetes patients who have hypoglycaemia unawareness, or unexplained discrepant HbA_{1c} and SMBG recordings. Should the need for CGM be deemed necessary, these patients should be referred to an endocrinologist for further assessment and management.

Authors: Larry A Distiller and Aslam Amod
Editor: Imran Paruk

References

1. World Health Organisation. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia: Report of a WHO/IDF Consultation. Geneva: WHO Press; 2006.
2. Standl E, Balletshofer B, Dahl B, et al. Predictors of 10-year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. Diabetologia. 1996;39(12):1540-1545.
3. Heine RJ, Balkau B, Ceriello A, Del Prato S, Horton ES, Taskinen M-R. What does postprandial hyperglycaemia mean? Diabet Med. 2004;21(3):208-213.
4. Goff DC, Gerstein HC, Ginsberg HN, et al. Prevention of Cardiovascular Disease in Persons with Type 2 Diabetes Mellitus: Current Knowledge and Rationale for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial. Am J Cardiol. 2007;99(12):S4-S20. doi:10.1016/j.amjcard.2007.03.002.
5. Gerstein HC, Pogue J, Mann JFE, et al. The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiological analysis. Diabetologia. 2005;48(9):1749-1755. doi:10.1007/s00125-005-1858-4.
6. Selvin E, Steffes MW, Zhu H, et al. Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults. N Engl J Med. 2010;362(9):800-811. doi:10.1056/NEJMoa0908359.

7. DeFronzo RA, Abdul-Ghani M. Assessment and Treatment of Cardiovascular Risk in Prediabetes: Impaired Glucose Tolerance and Impaired Fasting Glucose. Am J Cardiol. 2011;108(3):3B-24B. doi:10.1016/j.amjcard.2011.03.013.
8. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28(2):103-117.
9. Turner R. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-853. doi:10.1016/S0140-6736(98)07019-6.
10. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2008;358(24):2560-2572. doi:10.1056/NEJMoa0802987.
11. ACCORD Study Group, ACCORD Eye Study Group, Chew EY, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363(3):233-244. doi:10.1056/NEJMoa1001288.
12. Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. N Engl J Med. 2009;360(2):129-139. doi:10.1056/NEJMoa0808431.
13. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. N Engl J Med. 2008;359(15):1577-1589. doi:10.1056/NEJMoa0806470.
14. Orchard TJ, Nathan DM, Zinman B, et al. Association Between 7 Years of Intensive Treatment of Type 1 Diabetes and Long-term Mortality. JAMA. 2015;313(1):45. doi:10.1001/jama.2014.16107.
15. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of Intensive Glucose Lowering in Type 2 Diabetes. N Engl J Med. 2008;358(24):2545-2559. doi:10.1056/NEJMoa0802743.
16. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2008;358(24):2560-2572. doi:10.1056/NEJMoa0802987.
17. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology. Diabetes Care. 2009;32(1):187-192. doi:10.2337/dc08-9026.
18. American Diabetes Association. Glycemic Targets. Sec. 1. In Standards of Medical Care in Diabetesd2017. Diabetes Care. 2017;40(Supplement 1):S48-S56. doi:10.2337/dc17-S009.
19. Dluhy RG, McMahon GT. Intensive Glycemic Control in the ACCORD and ADVANCE Trials. N Engl J Med. 2008;358(24):2630-2633. doi:10.1056/NEJMe0804182.
20. Reaven PD, Moritz TE, Schwenke DC, et al. Intensive Glucose-Lowering Therapy Reduces Cardiovascular Disease Events in Veterans Affairs Diabetes Trial Participants With Lower Calcified Coronary Atherosclerosis. Diabetes. 2009;58(11):2642-2648. doi:10.2337/db09-0618.
21. Riddle MC, Ambrosius WT, Brillon DJ, Buse JB, Robert P. Epidemiologic Relationships Between A1C and All-Cause Mortality During a Medi ... Diabetes Care. 2010;33(May):983-990. doi:10.2337/dc09-1278.
22. Duckworth WC, Abraira C, Moritz TE, et al. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. J Diabetes Complications. 2011;25(6):355-361. doi:10.1016/j.jdiacomp.2011.10.003.
23. Zoungas S, Patel A, Chalmers J, et al. Severe Hypoglycemia and Risks of Vascular Events and Death. N Engl J Med. 2010;363(15):1410-1418. doi:10.1056/NEJMoa1003795.
24. Saremi A, Bahn GD, Reaven PD. A link between hypoglycemia and progression of atherosclerosis in the Veterans Affairs Diabetes Trial (VADT). Diabetes Care. 2016;39(3):448-454. doi:10.2337/dc15-2107.
25. Zoungas S, Chalmers J, Neal B, et al. Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes. N Engl J Med. 2014;371(15):1392-1406. doi:10.1056/NEJMoa1407963.
26. Perkovic V, Heerspink HL, Chalmers J, et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney Int. 2013;83(3):517-523. doi:10.1038/ki.2012.401.
27. Hayward R a., Reaven PD, Wiitala WL, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;372(23):2197-2206. doi:10.1056/NEJMoa1414266.
28. Gerstein HC, Beavers DP, Bertoni AG, et al. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. Diabetes Care. 2016;39(5):701-708. doi:10.2337/dc15-2283.
29. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-412. doi:10.1136/bmj.321.7258.405.
30. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010;340(jan08 1):b4909-b4909. doi:10.1136/bmj.b4909.
31. Gerstein HC, Miller ME, Ismail-Beigi F, et al. Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. Lancet (London, England). 2014;384(9958):1936-1941. doi:10.1016/S0140-6736(14)60611-5.
32. Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580-591. doi:10.1056/NEJMoa0706245.
33. Ismail-Beigi F, Moghissi E, Titken M et al. Individualising glycaemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Int Med. 2011;154:554-559
34. Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycaemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med. 2004;164:2147-2155.
35. DECODE Study Group, on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med. 2001;161: 397-405
36. Rodbard HW, Jellinger PS, Davidson JW. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus. Endocr Pract. 2009;15:540-559.
37. Guideline for management of postmeal glucose in diabetes. International Diabetes Federation Guideline Development Group. Diabetes Research and Clinical Practice, 103 (2014), pp. 256-268.
38. American Diabetes Association. Standards of Medical Care in Diabetes 2017. Diabetes Care. 2017: (Supp 1) 40;1-142
39. Nathan DM, Kuenen J, Borg R, et al; for the A1c-Derived Average Glucose (ADAG) Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care.2008;31:1473–1478.
40. Murata GH, Shah JH, Hoffman RM, et al. Intensified blood glucose monitoring improves glycemic control in stable, insulin-treated veterans with type 2 diabetes: The Diabetes Outcomes in Veterans Study (DOVES). Diabetes Care. 2003;26:1759-1768.
41. Sheppard P, Bending JJ, Huber JW. Pre- and post-prandial capillary glucose self-monitoring achieves better glycaemic control than pre-prandial only monitoring. A study in insulin treated diabetic patients. Practical Diabetes Int.2005;22:15-22.
42. Hans DJ. Postprandial or Fasting Hyperglycaemia: Time to move on? Diabetes Technology & Therapeutics. 2015;17:441-442
43. International Diabetes Federation. IDF Clinical Guidelines Taskforce and SMBG International Working Group. Global guideline on self-monitoring of blood glucose in non-insulin treated type 2 diabetes. International Diabetes Federation. c2009 [cited 2012 Mar 6]. Available from: http://www.idf.org/webdata/docs/SMBG_EN2.pdf.
44. Klonoff D, Bergenstal R, Blonde LS, et al Consensus report of the Coalition for Clinical Research -- self-monitoring of blood glucose. J Diabetes Sci Technol. 2008, 2:1030-1058.
45. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management - self-monitoring of blood glucose. NICE guidelines [NG28], December 2015. Available from: http://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations#self-monitoring-of-blood-glucose.
46. Davis WA, Bruce DG, Davis TME Is self-monitoring of blood glucose appropriate for all type 2 diabetic patients? The Fremantle Diabetes Study. Diabetes Care. 2006; 29:1764–1770.
47. Davis WA, Bruce DG, Davis TME Is self-monitoring of blood glucose appropriate for all type 2 diabetic patients? The Fremantle Diabetes Study. Diabetes Care. 2006; 29:1764–1770.
48. Kempf K, Kruse J, Martin S. ROSSO-in-praxi: a self-monitoring of blood glucose-structured 12-week lifestyle intervention significantly improves glucometabolic control of patients with type 2 diabetes mellitus. Diabetes Technology and Therapeutics. 2010;12:457-558.
49. Polonsky WH, Fisher L, Schickman CH, et al. Structured self- monitoring of blood glucose significantly reduces A1c levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the structured testing program study. Diabetes Care.2011;34:262-267.
50. Polonsky WH, Fisher L, Schickman CH, et al. The value of episodic, intensive blood glucose monitoring in non-insulin treated persons with type 2 diabetes: design of the Structured Testing Program (STeP) Study, a cluster-randomised, clinical trial [NCT00674986]. BMC Family Practice. 2010,11:37-47.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

9. Glucose Control: non-insulin therapies

This chapter summarises information for each of the non-insulin drug classes that are used for blood glucose control. Each summary is accompanied by a table of recommendations to guide the clinical use of these medications. For the sake of completeness, and for those that are interested, we have included a more detailed review of each drug as an appendix to each summary. These can be found in the Appendix section of the guidelines. The treatment recommendations for each drug have been incorporated into the treatment algorithm in Chapter 11. The following abbreviations are used in this chapter:
DPP-4: dipeptidyl peptidase-4
GLP-1: glucagon-like peptide-1

SGLT2- sodium-glucose linked transporter-2

9.1: Drug Summary – Metformin

SEMDSA Type 2 Diabetes Guideline Expert Committee

(Refer to appendix 9.1 for full text and references)

Mechanism of Action	Metformin targets the liver, skeletal muscle and the gut to reduce hepatic glucose output, increase skeletal muscle glucose uptake, increase GLP-1 levels and reduce glucose absorption.			
Glycaemic efficacy and indications	Mean HbA_{1C} reductions • As monotherapy vs. placebo: -1.1% • As add-on therapy to other non-insulin agents: -0.9% • Ass add-on to insulin: -0.6%			
Cardiovascular outcome trials	Proven superiority vs. diet alone in obese patients - reduced all-cause mortality, diabetes related mortality and myocardial infarction, but not peripheral vascular disease or microvascular disease. Proven superiority vs. SU and insulin in obese patients: reduced all cause mortality and stroke, but not myocardial infarction, diabetes-related deaths, peripheral vascular disease or microvascular disease. Safety when added to SU's (glibenclamide and chlorpropamide) is unclear.			
Hypoglycaemia	No severe hypoglycaemia as monotherapy. Some patients may have symptoms of hypoglycaemia. Can potentiate the hypoglycaemic effect of insulin or insulin secretagogues.			
Weight	Weight neutral or causes modest weight loss (-1.2kg). No weight loss in non-diabetic individuals.			
Non-glycaemic benefits	Improves lipid profile. Reduces cancer rates in population studies. May improve outcomes in mild to moderate heart failure; Improves laboratory measures of inflammation, coagulation, oxidative stress, endothelial function and tumour suppression; cancer rates are lower.			
Side Effects and Precautions	Gastrointestinal (GI) side-effects are common, are not dose-dependent, and occur in 20-30% of patients (diarrhoea, nausea, vomiting, cramping, bloating and flatulence). Up tp 10% will discontinue therapy due to GI side effects. Switching to an extended release formulation improves GI tolerability and adherence. Lactic Acidosis is rare with current usage (0.04 cases per 1000 patient years) and not different to non-metformin users. Metformin should be discontinued at the time of, or before an iodinated contrast imaging procedure or general anaesthesia in the following categories of patients: those with an eGFR < 60 mL/minute/1.73 m^2; those with a history of liver disease, alcoholism, or heart failure; those who will receive intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the procedure and restart metformin if renal function is stable and the patient is eating normally. Can cause low levels of serum vitamin B_{12} in 7-30% of long-term users, but is rarely associated with the clinical features of vitamin B_{12} deficiency. The exact mechanism and significance is unknown. There is no recommendation to screen for vitamin B_{12} deficiency routinely. Investigate and manage vitamin B_{12} deficiency according to standard clinical practice, with a high index of suspicion in patients who are vegetarian or anaemic, or have peripheral neuropathy.			
Dosing and prescribing	Metformin (standard release): Dose range is 500 mg/day to 3 000 mg/day in two or three divided doses with meals. Optimum glycaemic efficacy is achieved with 2 000 mg/day; few patients have additional glycaemic benefit with higher doses. The optimum dose for cardiovascular benefit in obese patients is 2 550mg/day. Metformin extended-release: Dose range is 500 mg/day to 2 000 mg/day as a single dose with the evening meal. The 2 000mg dose can be split to 1000mg twice daily without losing efficacy. Start with 500 mg/day of standard metformin tablets, and increase the dose by 500 mg every one to two weeks to minimise side effects. If GI side effects occur reduce the dose and re-titrate slowly. If GI disturbances persist try switching to the extended-release formulation.			
Renal dosing	**eGFR ≥60 ml/min** Standard dosing. Monitor eGFR annually	**45-60 ml/min** Standard dosing. Monitor eGFR 3 to 6 monthly	**30-45 ml/min** Maximum dose: 1000 mg/day Monitor eGFR 3 to 6 monthly	**< 30 ml/min** Metformin is contraindicated

SEMDSA 2017 Recommendations for metformin	
Initiate standard-release metformin therapy in all newly diagnosed obese patients with type 2 diabetes.	A
Initiate standard-release metformin therapy in all newly diagnosed non-obese patients with type 2 diabetes.	C
Dosing: Start with 500 mg once daily and up-titrate the dose slowly every 10 to 14 days until glycaemic targets are met or side effects occur. Few patients will achieve and maintain glycaemic targets with 500 mg once daily. Most patients will require1000 – 2550 mg per day in two or three divided doses. The optimum dose for cardiovascular benefit in obese patients is 2550 mg/day (850 mg TDS).	B
If gastrointestinal (GI) adverse events are limiting, try temporarily reducing or discontinuing the drug, and re-titrate when the GI disturbances resolve. The GI side-effects with metformin extended-release is not different to the standard release when used as initial therapy; however patients who switch due to the extended release may have improved tolerability. If GI disturbances remain intolerable with standard metformin tablets, try switching to a metformin extended release (XR) formulation and titrate the dose every 10-14 days again.	B
The extended release formulation should be dosed once daily with the evening meal at a dose not exceeding 2000 mg/day. The 2000 mg dose can be taken as 1000 mg twice a day without disadvantages if the patient so prefers. Patients not achieving their glycaemic target with 2000 mg of the extended release may benefit from switching to a higher dose of the standard release metformin.	B
Monitor renal function (eGFR) in all patients at least annually. Do not exceed 1000 mg/day if the eGFR is 30-45 ml/min/1.73m^2. Stop metformin therapy if the eGFR is < 30 ml/min/1.73m^2.	B
The significance of low serum vitamin B_{12} levels associated with long-term metformin use is not known. Measure and treat whenever clinically appropriate.	B
Profile of the patient in whom metformin may not be a preferred option: ◦ Patients with irritable bowel syndrome or other chronic gastrointestinal disorders ◦ Normal weight individuals who do not wish to lose weight ◦ Patients at high risk for lactic acidosis (severe heart, lung, liver, renal or peripheral vascular disease) ◦ There is a history of metformin intolerance.	C

Do not persist with any chosen treatment if the HbA_{1c} has not decreased by > 0.5% after six months

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

9.2: Drug Summary – Gliclazide modified-release

SEMDSA Type 2 Diabetes Guideline Expert Committee

(Refer to appendix 9.2 for full text and references)

Mode of action	Gliclazide modified-release is a sulphonylurea (SU) and insulin secretagogue that binds selectively to the sulphonylurea receptor-1A (SUR1A) binding-site of K_{ATP} channels on pancreatic beta cells resulting in membrane depolarization, calcium influx and exocytosis of stored insulin.
Glycaemic efficacy and indications	When used as monotherapy or as add-on to other non-insulin glucose lowering drugs the mean HbA_{1C} reduction is -1% with sustained efficacy beyond 2 years.
Cardiovascular outcome trials	The ADVANCE study, using a gliclazide modified-release intensive treatment strategy achieved an HbA_{1C} target of 6.5% (vs. 7.3% for conventional treatment) and demonstrated a significant reduction in microvascular outcomes (and therefore also the combined microvascular and macrovascular outcomes), driven mainly by the reduction in the incidence of nephropathy. There have been no dedicated cardiovascular safety studies with any sulphonylurea. Meta-analyses of observational and randomized controlled trials consistently demonstrate that gliclazide has a better cardiovascular safety profile than glibenclamide and glimepiride.
Hypoglycaemia	Gliclazide modified-release increases the risk of hypoglycaemia when used as monotherapy or combination therapy, but this is significantly lower when compared to glibenclamide and glimepiride. The rates of hypoglycaemia increase with lower glycaemic targets.
Weight	Weight change ranges from 0 to +1.5 kg. Mean weight gain in a meta-analysis of RCTs was 0.5kg.
Non-glycaemic benefits	Gliclazide modified-release increases peripheral insulin sensitivity, decreases hepatic glucose production, inhibits platelet aggregation and adhesion, increases t-PA activity and has antioxidant effects. There are also reports of possibly a lower cancer risk compared to other SUs and insulin.
Side Effects and Precautions	Side-effects apart from hypoglycaemia and weight gain are rare. Cross-reactivity with sulphonamide antibiotic allergy is uncommon and is not a contra-indication. Do not use with advanced liver disease because of hepatic metabolism.
Dosing and prescribing	• The usual starting dose for gliclazide modified-release is 30 to 60 mg administered once daily with the morning meal. • Consider starting with the higher (60 mg) dose when the HbA_{1C} target is more than 0.5% from the prevailing HbA_{1C} level, or if the patient is has symptomatic hyperglycaemia. • The dose can be escalated by 30 to 60mg every one to four weeks, guided by fasting glucose levels. • The maximum dose is 120 mg administered once daily with the morning meal. • If mild hypoglycaemia occurs unexpectedly reduce the dose by 30 to 60 mg. • A single episode of severe hypoglycaemia or recurrent episodes of mild hypoglycaemia would be a strong indication to switch to an alternative glucose lowering drug. • The 60 mg tablets are scored and can be broken to improve cost effectiveness.
Renal dosing	Current guidelines recommend that gliclazide modified-release can be used at all stages of chronic kidney disease using standard dosing guidelines. Caution is advised however, when the eGFR is < 30 ml/min/1.73m^2, and these patients with CKD stage 3 or worse should be managed with specialist supervision.
Cost of cheapest formulation at maximum dose	R93.00 for 120 mg (Single exit price as at March 2017).

SEMDSA 2017 Recommendations for sulphonylureas	
The sulphonylurea of choice should be gliclazide modified-release because: ◦ It has equivalent efficacy compared to other sulphonylureas. ◦ It is consistently associated with lower rates of hypoglycaemia and better cardiovascular and renal safety relative to other sulphonylureas. ◦ It has proven benefits for long-term microvascular disease outcomes.	A
Glibenclamide must not be used at primary care level.	A
Consider gliclazide modified-release as initial monotherapy when metformin is not tolerated or is contraindicated.	B
Consider gliclazide modified-release as add-on (dual therapy) to metformin (or other initial drug therapy) in most patients not achieving or maintaining their glycaemic targets.	A
If not already in use, consider gliclazide modified-release as a third glucose lowering drug.	A
To convert treatment from another sulphonylurea to gliclazide modified-release, use the following dose conversion: ◦ Glibenclamide 5 mg ≈ Gliclazide modified-release 30 mg ◦ Glimepiride 1-2 mg ≈ Gliclazide modified-release 30 mg	C
Only continue gliclazide modified-release beyond stage 3 chronic kidney disease (when the eGFR is less 30 ml/min/m^2) with specialist supervision.	C
Circumstances where gliclazide MR may be preferred to other treatment options: ◦ Gliclazide MR should be the preferred second drug for the majority of patients with type 2 diabetes. ◦ At diagnosis when rapid control of hyperglycaemic symptoms is required.	C
Circumstances where gliclazide MR may not be the preferred option: ◦ The individualised glycaemic target is ≤ 6.5% (as the risk of hypoglycaemia may be unacceptably high with this target). ◦ There is a history of severe hypoglycaemia or hypoglycaemia unawareness. ◦ There is a history of recurrent hypoglycaemia (any degree) despite dose adjustments. ◦ The risk of hypoglycaemia is high and/or its consequences are severe. ◦ The patient has advanced liver disease.	

Do not persist with any chosen treatment if the HbA_{1c} has not decreased by > 0.5% after six months

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

9.3: Drug Summary – Pioglitazone

SEMDSA Type 2 Diabetes Guideline Expert Committee

(Refer to appendix 9.3 for optional full text and references)

Mode of action	Agonist of nuclear receptors called peroxisome proliferator-activated receptor-gamma (PPARγ). Leads to increased transcription of proteins that augment the post-receptor actions of insulin resulting in improved insulin sensitivity and ß-cell function.
Glycaemic efficacy and indications	Good efficacy as monotherapy, dual therapy and triple therapy (± 1% HbA_{1C} reduction); similar efficacy to metformin, SU or GLP-1RA.
Cardiovascular outcome trials	PROactive study (secondary prevention) showed reductions in secondary endpoints (composite of all-cause mortality, non-fatal myocardial infarction, and stroke) by 16%. Meta-analysis of RCTs also reported a significant 18% relative risk reduction in the composite outcome (death, myocardial infarction, or stroke). Increases heart failure hospitalisations because of fluid retention, but not mortality.
Hypoglycaemia	Does not cause hypoglycaemia except when combined with insulin or insulin secretagogues.
Weight	Causes dose-dependent weight gain (~2-4 kg) due to fluid retention and adipocyte differentiation. Weight gain correlates with therapeutic response.
Non-glycaemic benefits	Increases HDL-C; reduces triglycerides, reduces LDL atherogenicity, CRP and microalbuminuria; increases PAI-1 and adiponectin; reduces carotid intima media thickness and atheroma volume. Reduces hepatic fibrosis in non-alcoholic steatohepatitis (NASH); improves ovulation and metabolic abnormalities in polycystic ovary syndrome.
Side Effects and Precautions	Can cause fluid retention, oedema, and may worsen or precipitate congestive heart failure. Associated with an increase in distal long-bone fractures in women and men. Possible small increase in bladder cancer.
Dosing and prescribing	Start with 15 once daily in the morning; increase to 30 mg after one to three months if necessary. Most patients will derive optimum benefit at this dose; do not exceed 30 mg in the primary care setting. Maximum registered dose is 45 mg daily.
Renal dosing	No dose adjustment is necessary, but do not use if renal disease is causing fluid retention, or when the eGFR is <30 ml/min/1.73m^2.
Cost of cheapest formulation	R117.00 for 30 mg.

SEMDSA 2017 Recommendations for pioglitazone	
Consider pioglitazone as initial monotherapy when metformin is contraindicated or not tolerated.	A
Consider pioglitazone as add-on to metformin or other initial drug therapy, in selected patients not achieving or maintaining their glycaemic targets.	A
Consider pioglitazone as a third non-insulin glucose lowering drug in selected patients not achieving or maintaining their glycaemic targets on an existing oral two-drug regimen.	A
Circumstances where pioglitazone may be preferred to other treatment options: ◦ Gliclazide MR is contraindicated or not tolerated. ◦ Non-alcoholic steatohepatitis is present. ◦ The patient has features of severe insulin resistance. ◦ There is a history of previous myocardial infarction, previous stroke or chronic kidney disease stage-3 (pioglitazone offers probable benefit for secondary prevention)	C
Circumstances where pioglitazone may not be the preferred option: ◦ Age > 75 years old (risk of congestive heart failure (CHF), fracture and bladder cancer) ◦ History of congestive heart failure. ◦ History of osteoporosis. ◦ History of bladder cancer, or haematuria that has not been investigated. ◦ Stage-4 or worse chronic kidney disease (risk of fluid retention). ◦ Patients on insulin therapy (higher risk of fluid retention and CHF). ◦ Elevated liver enzymes (>2x ULN), which is not due to NASH.	C

Do not persist with any chosen treatment if the HbA_{1C} has not decreased by > 0.5% after six months

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

9.4: Drug summary - DPP-4-inhibitors

SEMDSA Type 2 Diabetes Guideline Expert Committee

(Refer to Appendix 9.4 for review and references)

Mode of action and pharmacology	DPP-4 inhibitors (gliptins) are capable of inhibiting the degradation of endogenous GLP-1, thereby therapeutically raising circulating GLP-1 levels.			
Glycaemic efficacy and indications	Can be used as monotherapy in selected patients when there is intolerance to metformin (where there is a high risk for hypoglycaemia). Can be used as dual or triple therapy when added to metformin / sulphonylurea / SGLT 2 inhibitor / insulin. HbA_{1C} reduction when used as monotherapy is between 0.5 and 1.1 %.			
Macrovascular and Mortality Outcomes	Cardiovascular outcome safety trials for all 3 DPP-4 inhibitors have been neutral for major adverse cardiovascular events. Saxagliptin was associated with increased rates of hospitalisation for heart failure.			
Hypoglycaemia	Hypoglycaemia rates are not different to placebo except when DPP 4 inhibitors are combined with insulin or insulin secretagogues.			
Non-glycaemic benefits	Weight-neutral.			
Side Effects and Precautions	Small absolute risk for pancreatitis. Increased risk of hospitalisation for heart failure with saxagliptin.			
Contraindications	Acute, chronic or recurrent pancreatitis or high risk for pancreatitis. Pancreatic cancer. All are contraindicated in severe liver disease. Use saxagliptin and vildagliptin with caution in moderate liver disease. Heart failure (saxagliptin).			
Dosing	*eGFR*	**Saxagliptin**	**Sitagliptin**	**Vildagliptin**
	≥50 ml/min	5 mg daily	100 mg daily	50 mg twice a day
	30-50 ml/min	2.5 mg daily	50 mg daily	50 mg daily
	<30 ml/min	2.5 mg daily	25 mg daily	50 mg daily
Cost at maximum dose	Moderate (R260 – 340 per month - single exit pricing as at March 2017)			

SEMDSA 2017 Recommendations for DPP-4 inhibitors	
Consider a DPP-4 inhibitor as initial monotherapy when metformin is contraindicated or not tolerated.	C
Consider a DPP-4 inhibitor as add-on to metformin or other initial drug therapy, in selected patients not achieving or maintaining their glycaemic targets.	A
Consider a DPP-4 inhibitor as the third glucose lowering drug in selected patients not achieving or maintaining their glycaemic targets on an existing oral two-drug regimen.	A
Combination DPP-4 inhibitor and insulin therapy should be initiated at specialist level.	C
Be aware of dose adjustments for chronic kidney disease.	C
Circumstances where a DPP-4 inhibitor may be preferred to other treatment options: ◦ As the 2nd add-on drug when gliclazide MR is contraindicated or not tolerated. ◦ As the 3rd add on drug for most patients if HbA_{1C} targets are potentially achievable. ◦ Older patients with multiple comorbidities. ◦ Patients with stage-4 chronic kidney disease (can be used without risk of hypoglycaemia). ◦ If a fixed-dose combination tablet will improve adherence, compliance and/or cost-effectiveness.	C
Circumstances where a DPP-4 inhibitor may not be the preferred option: ◦ Very high HbA_{1C} and the glycemic target is not likely to be achieved with a DPP-4 inhibitor. ◦ History of pancreatitis or pancreatic tumour. ◦ History of heart failure or high risk of heart failure (saxagliptin). ◦ Liver disease: moderate (do not use saxagliptin or vildagliptin) or severe (do not any DPP-4 inhibitor).	C

Do not persist with any chosen treatment if the HbA_{1C} has not decreased by > 0.5% after six months

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

9.5: Drug summary - GLP-1 receptor agonists

SEMDSA Type 2 Diabetes Guideline Expert Committee

(Refer to Appendix 9.5 for drug review and references)

Mode of action and pharmacology	GLP-1 receptor agonists are modified GLP-1 molecules that have structural homology with endogenous GLP-1 but are resistant to the enzymatic cleavage by DPP-4.		
Glycaemic efficacy and indications	Reduces HbA_{1C} by 0.9 to 1.2 %. Monotherapy: registered (liraglutide) but not recommended for primary healthcare. Dual therapy: registered but not recommended for primary healthcare. Triple therapy: Can be combined with any 2 of metformin / sulphonylurea / TZD. Do not combine with DPP-4 inhibitor or SGLT2 inhibitor. Exenatide can be as added to basal insulin with or without oral agents.		
Macrovascular and Mortality Outcomes	Lixisenatide was neutral in the ELIXA trial. Liraglutide and semaglutide have each demonstrated reductions in a composite endpoint of major adverse cardiovascular events by 13% and 26% in the LEADER and SUSTAIN-6 trials respectively (vs. placebo), when used in patients with established cardiovascular disease. There are no cardiovascular outcomes trials with exenatide.		
Hypoglycaemia	Hypoglycaemia rates are not different to placebo except when GLP-1 receptor agonist are combined with insulin or insulin secretagogues.		
Non-glycaemia benefits	Weight reduction of between 1 and 3 kg for exenatide and liraglutide. Both exenatide and liraglutide reduce SBP and DBP by 1 to 5 mmHg. Reduction in liver fat content (liraglutide).		
Side Effects and Precautions	Nausea and vomiting in up to 25%; Discontinuation rate 5-20%. Pancreatitis. Skin reactions.		
Contraindications	History of pancreatitis, or at high risk for pancreatitis (e.g. untreated gallstone disease, recent or planned ERCP, excessive alcohol use). History of pancreatic tumour. History of medullary thyroid cancer (MTC) or multiple endocrine neoplasia (MEN) syndrome type 2		
Dosing	*eGFR*	**Exenetide**	**Liraglutide**
	≥30 ml/min	Initial dose is 5 ug BD for the 1st month; then 10 ug BD	Initiate 0.6 mg daily Maximum dose of 1.8 mg daily
	<35 ml/min	Contraindicated	No adjustment
Cost	High (R620.00 to R2145.00 - single exit price March 2017)		

SEMDSA 2017 Recommendations for GLP-1 receptor agonists (GLP-1RA)	
Consider a GLP-1RA injectable as the third glucose lowering drug (triple therapy) in overweight and obese patients when glycaemic targets are not being achieved or maintained.	A
Consider adding a GLP-1RA to existing basal insulin therapy (with oral therapies) as an alternative to intensifying the insulin regimen, especially when weight gain and/or hypoglycaemia is a limiting factor.	A
Escalate the dose of GLP-1RA slowly to minimise side-effects.	C
Circumstances where a GLP-1RA may be preferred to other treatment options: ◦ Overweight and obese patients ◦ Weight gain or hypoglycaemia has been, or is likely to be problematic with other treatment options. ◦ HbA_{1C} is very high (GLP-1RA and insulin are the most effective glucose lowering drugs for most patients). ◦ Patients with established cardiovascular disease (liraglutide benefit); to be managed at specialist care level.	C
Circumstances where a GLP-1RA may not be the preferred option: ◦ Patients with chronic gastrointestinal disorders. ◦ Patients with a history of pancreatitis or pancreatic tumour.	C

Do not persist with any chosen treatment if the HbA_{1C} has not decreased by > 0.5% after six months

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

9.6: Drug Summary - SGLT2 inhibitors

SEMDSA Type 2 Diabetes Guideline Expert Committee

(Refer to Appendix 9.6 for review and references)

MOA	By inhibiting SGLT2, gliflozins reduces renal glucose reabsorption, leading to increased urinary excretion of excess glucose and a reduction in plasma glucose concentrations in a non-insulin dependent manner.			
Glycaemic efficacy and indications	As monotherapy: 0.6% to -1.2%; non-inferior to metformin. As add on to metformin: -0.5% to -1.0%; non-inferior to other classes As add on to metformin + SU: -0.7% to -0.9%; non-inferior to DPP-4 inhibitors As add on to insulin therapy: -0.5% to -0.8%			
Microvascular Outcomes	No primary outcome studies.			
Macrovascular and Mortality Outcomes	Empagliflozin therapy was associated with a reduction in all-cause death, cardiovascular-death and hospitalisation for heart failure in patients with established cardiovascular disease. There has been no signal of adverse cardiovascular outcomes in systematic meta-analyses for the other SGLT2 inhibitors.			
Hypoglycaemia	Hypoglycaemia rates are not different to placebo except when SGLT2 inhibitors are combined with insulin or insulin secretagogues.			
Non-glycaemic benefits	Mean weight loss of 1.6 to 2.5 kg; not different to GLP-1RAs (meta-analysis) Systolic and diastolic blood pressure reduction (-4.0 and -1.5 mmHg) respectively.			
Side effects and precautions	Mycotic genital infections are common (and more so in women); do not use in patients with a history of recurrent genital infections. The risk of urinary tract infections may be increased but can be minimised by advising adequate hydration and fastidious bathroom hygiene; do not prescribe SGLT2 inhibitors in patients with a history of recurrent UTI. Dehydration and hypotension can occur particularly in susceptible patients (treated with loop diuretics, have advanced cardiac disease or older than 65 years). Always ensure and emphasise adequate hydration when prescribing SGLT2 inhibitors. eGFR usually declines within the first weeks of initiating therapy and then gradually returns toward baseline. Monitor eGFR and discontinue SGLT2 inhibitors if the decline is ≥ 30%. Diabetic ketoacidosis may occur at mildly elevated levels of blood glucose particularly in insulin treated patients. Warn patients of the symptoms of DKA and advise them to seek medical attention immediately. The risk of fractures and lower-limb (especially toe) amputations is increased with canagliflozin. Therefore do not use canagliflozin, and exercise caution with the other drugs in this class, in patients who are at high risk for these conditions. Do not prescribe dapagliflozin to patients with bladder cancer or in combination with pioglitazone.			
Dosing	*eGFR*	**Dapagliflozin**	**Empagliflozin**	**Canagliflozin**
	≥60 ml/min	5 mg or 10 mg	10 mg or 25 mg	100 mg or 300 mg
	45-60 ml/min	Contraindicated	Continue 25 mg but do not initiate therapy	Continue 100 mg but do not initiate therapy
	<45 ml/min	Contraindicated	Contraindicated	Contraindicated
Cost	Unknown; not registered in South Africa as at March 2017.			

SEMDSA 2017 Recommendations for SGLT2 inhibitors	
Do not use SGLT2 inhibitors as initial monotherapy	C
Consider a SGLT2 inhibitor as add-on (dual therapy) to metformin (or other initial drug therapy) in selected patients not achieving or maintaining their glycaemic targets.	A
Consider a SGLT2 inhibitor as the 3rd glucose lowering drug in selected patients not achieving or maintaining their glycaemic targets on an existing oral two-drug regimen.	A
Circumstances where an SGLT2inhibitor may be preferred to other treatment options: ◦ Overweight and obese patients. ◦ Weight gain or hypoglycaemia has been, or is likely to be problematic with other treatment options. ◦ Patients with established cardiovascular disease (empagliflozin benefit); to be managed at specialist care level.	
Circumstances where an SGLT2 inhibitor may not be the preferred option: ◦ Patients with recurrent mycotic genital infections or urinary tract infections. ◦ Patients at risk for dehydration and hypotension. ◦ Patients at high risk for stroke, fracture (canagliflozin), amputation (canagliflozin), bladder cancer (dapagliflozin) or ketoacidosis (refer to drug review).	C
Do not initiate SGLT2 inhibitors when the eGFR is < 60 ml/min/m^2.	
Stop all SGLT2 inhibitors when the eGFR is < 45 ml/min/m^2.	

Do not persist with any chosen treatment if the HbA_{1c} has not decreased by > 0.5% after six months

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

9.7: Alpha-glucosidase inhibitors (acarbose)

SEMDSA Type 2 Diabetes Guideline Expert Committee

Mechanism of Action	Prevents the conversion of complex carbohydrates into monosaccharides within the intestine thereby decreasing the ability to absorb monosaccharides.	
Glycaemic efficacy and indications	HbA_{1C} reduction when used as monotherapy of between 0.6 and 0.8%.	A
Microvascular Outcomes	Reduction of Microvascular Complications are inferred from the benefit of improved glycaemic control.	B
Macrovascular and Mortality Outcomes	Acarbose significantly reduced the risk of cardiovascular events by 49% in patients with impaired glucose tolerance. No data for patients with Diabetes.	B
Hypoglycaemia	Hypoglycaemia rates are no different to placebo except when combined with Insulin or Insulin Secretagogues.	B
Non glycaemic benefits	Weight neutral.	B
Side Effects and Precautions	Transient elevation of hepatic transaminases.	B
	Gastrointestinal Side Effects (Flatulence and diarrhoea).	B
Dosing	*eGFR*	**Acarbose**
	≥30 ml/min	Start with 50 mg once daily with meals, and increase by 50 mg every two weeks if tolerated. Maximum dose is 100 mg x3 daily.
	<30 ml/min	Not recommended
Cost	High (R407.00).	

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Chapter 10: Glucose control: insulin therapy

SEMDSA 2017 Type 2 Diabetes Guidelines Expert Committee

Drug Summary – Insulins

(Refer to Appendix 10.1 for a detailed review of insulin therapy)

Mode of action	Insulin and its analogues lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.
Glycaemic efficacy and indications	Efficacy is theoretically unlimited but in practice may be limited by inadequate education and support, or by side effects (weight gain and hypoglycaemia). Insulin should be used in patients with features of metabolic decompensation (catabolic features, severe hyperglycaemia (fasting glucose > 14 mmol/L, random glucose > 16.5 mmol/L or a HbA_{1c} > 10%) or persistent ketosis at any stage of the disease. Insulin should be considered as one of the therapeutic options in patients not achieving adequate glycaemic control on 2 or 3 oral glucose lowering drugs.
Cardiovascular outcome trials	• UKPDS 10-year observational extension showed a decrease in myocardial infarction in the group where treatment had been intensified using insulin or a sulphonylurea • The ORIGIN trial did not show cardiovascular benefit when using a basal insulin analogue in patients with diabetes or intermediate dysglycaemia; it was neutral. • Multiple studies and meta-analyses suggest that insulin may be associated with adverse cardiovascular outcomes when compared to comparators (metformin and sulphonylureas).
Hypoglycaemia	When used as monotherapy, dual therapy or triple therapy most studies show that the addition of insulin increases the risk of hypoglycaemia. The rates of overall and nocturnal hypoglycaemia are lower with long-acting basal insulin analogues when compared to intermediate human insulins (NPH). Analogue basal insulins are preferred when hypoglycaemia is a limiting factor to achieving glycaemic control.
Weight	When used as monotherapy or as add on to oral hypoglycaemic agents most studies show that insulin causes weight gain. Weight gain over three years in the 4T study was 3.6 kg for basal and 5.7 kg for premix insulin. Insulin detemir, however, has been shown in a few studies to either be weight neutral or result in some weight loss in those patients that are overweight or obese.
Non-glycaemic benefits	Insulin also promotes protein synthesis, lipogenesis and increases the permeability of cells to potassium, magnesium and phosphate ions.
Side Effects and Precautions	• Fluid retention, oedema • Lipodystrophy • Local allergy • Systemic allergy • Existing cardiovascular disease: there is no evidence for the cardiovascular safety of insulin in patients with established cardiovascular disease, and some studies suggest a possible harmful effect. Avoiding hypoglycaemia takes precedence over intensive glycemic control in these patients.
Dosing and prescribing	Starting doses: • Basal insulin: Start 10 u at bedtime; monitor fasting glucose; educate the patient to titrate the dose using one of the titration algorithms to achieve fasting glucose targets (refer to Chapter 11, figure 2). • Premix insulin: When escalating from a basal insulin regimen to a premix regimen, administer two-thirds of the total basal insulin dose in the morning, and one-third in the evening. Educate the patient to titrate the doses using one of the titration algorithms to achieve pre-prandial glucose targets (refer to Chapter 11, figure 2). • Prescription for insulin must be accompanied with education about handling, storage, injection technique, injection sites, monitoring, titrating and the detection and management of hypoglycaemia.
Renal dosing	All insulin preparations are metabolised by the kidneys and will therefore require a dose reduction in patients with renal impairment.
Cost	Cost is variable depending on insulin type and dose, and is generally more expensive than oral agents. Refer to Appendix 10.2 for a complete list of insulins and prices.

SEMDSA 2017 Recommendations	
Consider insulin as first-line therapy at diagnosis, and at any other point in the course of the disease, in the setting of metabolic decompensation with any of the following features: a. Catabolism (marked weight loss) b. Fasting plasma glucose levels >14 mmol/l c. Random glucose levels consistently >16.5 mmol/l d. HbA_{1c} > 10% e. Presence presence of persistent ketogenesis, ketoacidosis or or hyperosmolar non-ketotic state.	C
If insulin is needed at diagnosis, use either pre-mixed insulin twice daily or basal bolus intensive insulin therapy (specialist referral is recommended)	A
Initial insulin therapy at diagnosis is usually temporary, and most patients can be weaned off their insulin with the addition of oral agents. If the patient is not able to transition from insulin to oral therapy reconsider the diagnosis of type 2 diabetes, and refer to a specialist if in doubt.	C
Consider adding basal insulin as the third glucose lowering drug in patients not achieving or maintaining their glycaemic targets on a two-drug oral regimen, especially if targets are unlikely to be achieved with other third line options, and there are adequate resources to support insulin initiation and titration.	B
Insulin therapy must be accompanied with intensive patient education and support, which includes (but is not limited to) SMBG and titration instructions, as well as education about the risk of hypoglycaemia.	B
Analogue insulins offer some advantages over human insulins and are therefore preferred when the acquisition cost is similar.	C
If nocturnal hypoglycaemia is a limiting factor to achieving optimal glycaemic control, consider switching from a human basal insulin to an analogue basal insulin, such as insulin glargine or insulin detemir.	B
If glycaemic targets are not being met despite adequate titration of basal insulin, consider combination injectable therapies using a premix, a basal-plus (prandial insulin) or a basal insulin plus GLP-1 receptor agonist combination. Consider the advantages and disadvantages of each option for each individual patient.	B
Be aware that insulin therapy is associated with the highest rates of hypoglycaemia and weight gain when compared to other glucose lowering drugs. However this is not a reason to delay or withhold insulin therapy when it is needed.	A
Consider referring a patient to an endocrinologist or specialist physician when: ◦ Glycaemic targets are unmet with basal insulin doses > 0.8 u/kg or > 60 u daily. ◦ Glycaemic targets are unmet after 6 months of treatment ◦ There is a need for a basal bolus insulin regimen ◦ Glycaemic targets are unmet with premix insulin doses > 60 u twice daily.	C
◦ Choice of insulins: insulins with the lowest acquisition cost within each class are preferred. In each insulin class an insulin analogue is the preferred option if the acquisition cost is similar to that of a human insulin. Registered biosimilar preparations are safe and effective. The newer insulins, such as ultra-long acting premixes and U300 concentrated insulins, are not recommended for use at primary care level.	C

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 11: The approach to achieving glycaemic control

SEMDSA 2017 Type 2 Diabetes Guidelines Expert Committee

Type 2 diabetes is a heterogeneous disease, with the underlying mechanism ranging from predominantly insulin resistance with relative insulin deficiency, to predominantly an insulin secretory defect with lesser degrees of insulin resistance. The relative contribution of each abnormality varies between individuals, as well as within the same individual at different stages of the disease. *People* with type 2 diabetes are heterogeneous; diabetes is prevalent across all socio-economic strata, ethnic groups, age groups and weight categories, in individuals with highly variable nutrient intakes and levels of physical activity.[1] In addition to phenotypic heterogeneity, there is *genetic variability* which may play a role in susceptibility, both to the disease itself or its complications.[2] The *response to treatment* is heterogeneous; we see diversity in responses to the same treatments even in patients with near-identical phenotypes. It seems intuitive then, that a single uniform approach to management of such a heterogeneous disorder is unlikely to be successful. The optimal pharmacological approach to glucose control for any individual patient varies, which is why many international guidelines have endorsed individualised management, with no restriction on the choice of glucose lowering drug after initial metformin therapy.[3–7] The concept of patient-centred care incorporates patients as partners in their healthcare. In practice, this means providing care that is "respectful of and responsive to individual patient preferences, needs and values, and ensures that patient values guide all clinical decisions".[3] These guidelines also have a broad target audience that includes health care professionals at all levels of expertise.

The SEMDSA approach to glycaemic control does not lose focus of patient-centred care but attempts to provide guidance about appropriate therapeutic choices for primary healthcare practitioners managing patients at different stages of type 2 diabetes. This is done by attempting to match the therapeutic options with the diverse clinical profiles encountered in patients, while still offering a rational approach to drug management. In the South African healthcare system, with its shortage of doctors, it is also important that nurses at primary healthcare clinics have access to medicines with the lowest probability of harm.

11.1 Factors to consider when choosing glucose lowering drugs

The factors that need to be considered when choosing appropriate pharmacologic therapies to match individual patient

Figure I: Some of the factors to consider when choosing glucose lowering drug therapy at various stages of type 2 diabetes

	Gliclazide modified release	Pioglitazone	DPP-4 inhibitor	GLP-1 receptor agonist	SGLT2 inhibitor	Basal insulin
Mean HbA_{1C} reduction	-0.8 to -1.0%	-0.8 to -1.0%	-0.7%	-0.8 to -1.2%	-0.8 to -1.0%	-0.8 to -1.2%
Hypoglycaemia (monotherapy)	Yes	Rare	Rare	Rare	Rare	Yes
Hypoglycaemia (added to SU)	-	++	+	+	+	++
Weight change	+0.0 to 1.5kg	+3.0 to 5.0 kg	Neutral	-3.0 kg	-3.0kg	+3-5kg
Adverse events*	None	Fluid retention (oedema, CHF)	Heart failure with saxagliptin	Common – GI upset	Common - GU infection Dehydration	Local skin reactions
Rare SAEs	None	Fractures, ?bladder cancer	Pancreatitis, pancreatic cancer	Pancreatitis, pancreatic cancer	Fractures Amputation DKA	None
Treatment complexity	Low	High	Low	Intermediate	High	High
Cardiovascular benefit	None	Yes, 1^{O} and 2^{O} prevention	None	Yes (2^{O} prevention)	Yes (2^{O} prevention)	None
Cost#	<R100	R120-180	R250-350	R650-2150	Unknown	R200 to >1000§
Initiate at	1^{st} or 2^{nd} Line	1^{st} or 2^{nd} Line	1^{st} or 2^{nd} Line	3^{rd} Line	2^{nd} Line	3^{rd} Line

*Side effects other than weigh gain and hypoglycaemia; GI=gastrointestinal; GU= genitourinary; SU = sulphonylurea; SAEs= serious adverse events

Information represents a synthesis of data from various sources discussed in the text.
#Cost is based on single exit price in the private health sector; figures may differ in the public health sector. §Cost of insulin depends on dose, and excludes ancillary costs. In the 4T study basal insulin dose ranged from 0.5u/kg to 1.0u/kg from year 1 to year 3.[8]though evidence supporting specific insulin regimens is limited. Methods In an open-label, controlled, multicenter trial, we randomly assigned 708 patients with a suboptimal glycated hemoglobin level (7.0 to 10.0% This translates to 40 to 80u/day for intensive basal insulin therapy in an 80kg person.
*Adverse events refer to common side effects (other than weight gain and hypoglycaemia) that impact tolerability and drug discontinuation rates.
Treatment complexity considers the ease with which the drug can be prescribed; higher complexity may demand greater resources (consulting time or other resources) in screening for contraindications, educating the patient about the treatment or the patient's required investment in complying with the treatment (e.g. injecting, SMBG and dose titration), as well as resources to monitor and treat adverse effects.

needs, fears and comorbidities are many, and are summarised in Figure I. These are also the factors that were considered when formulating the algorithm for the management of hyperglycaemia.

a. Glycaemic targets

The importance of individualised glycaemic targets, and the factors to consider, are covered in Chapter 8. These range from an HbA_{1C} < 6.5% for younger newly diagnosed patients with no comorbidities and long life expectancy, to 8.5% for the frail patient with multiple comorbidities and shorter life expectancy. In general though, the glycaemic target for the majority of patients should be an HbA_{1C} ≤ 7.0%.

b. Glycaemic efficacy

This is probably less of a consideration than in the past. All of the drug options are efficacious at lowering blood glucose and the reductions obtained with monotherapy are generally greater than those obtained with combination therapy for the same drug. Maximum glucose lowering efficacy is usually evident by six months. A meta-analysis of the various drug choices show that most will reduce HbA_{1C} by approximately 0.8 to 1.2%, without much difference between all of the available agents, when added to metformin.[9–12] For triple therapy (adding to metformin + sulphonylurea), the most effective 3rd line drugs appear to be basal insulin, followed by TZDs, GLP-1RA and SGLT2 inhibitors equally, with DPP-4 inhibitors having the greatest odds of treatment failure.[10] Again the differences are not large.

Also, in clinical practice the range of HbA_{1C} reduction for each drug is wide, with some patients responding very well, and others not responding at all to a particular drug. Baseline HbA_{1C} also determines glycaemic efficacy; a 1% higher baseline HbA_{1C} predicts an additional -0.5% HbA_{1C} reduction at six months.[12] To illustrate this point, in a study analysing patients with high baseline HbA_{1C}, empagliflozin 25 mg reduced the HbA_{1C} by 3.3% from a baseline HbA_{1C} of 11.1%.[13] The ability of a patient to concurrently intensify lifestyle measures is also important when intensifying drug therapy. In clinical practice, the combination of these interventions has been known to dramatically reduce HbA_{1C} levels to an extent far greater than published mean HbA_{1C} reductions.

The variability in glycaemic efficacy within each drug class, and between drug classes in patients with similar phenotypes, together with the small absolute differences between agents, suggests that the choice of glucose lowering drug should probably be based on other patient factors (Figure I), which are more likely to impact treatment success or failure, rather than glycaemic efficacy alone. In any event, the efficacy of any added therapy must be assessed within six months; failure to achieve the target and reduce the HbA_{1C} by ≥ 0.5% should prompt a change to an alternative drug.

c. Hypoglycaemia

Treatment-related hypoglycaemia is the commonest form of hypoglycaemia, and is a function of insulin or insulin sulphonylurea use. This topic is covered in Chapter 12. Hypoglycaemia is an important consideration when choosing therapies because it can have a significant negative impact on a person's wellbeing and quality of life, and can influence adherence, compliance, and therefore the success of treatment. Severe hypoglycaemia emerges as one of the strongest risk factors for cardiovascular events and mortality, especially in those patients with higher cardiovascular risk.[14–19] Independent risk factors for severe hypoglycaemia are listed in Figure II. The circumstances where the consequences of severe hypoglycaemia are sufficiently severe to warrant the avoidance of hypoglycaemia-inducing drugs are listed in Figure III.

Figure II: Independent risk factors for severe hypoglycaemia[17,20]

Insulin or sulphonylurea use
Intensive glucose control
Use of 2 or more oral glucose lowering drugs
Older age
Diabetes duration
Hypoglycaemia unawareness
Impaired cognitive function
Low body mass index
Renal impairment
Microvascualr complications

Figure III: Circumstances where the consequences of hypoglycaemia may be catastrophic

Operators of heavy machinery
Scaffold workers
Drivers of public transport or heavy duty vehicles
Airline pilots
Emergency rescue workers
People who live alone and have impaired cognition or mobility (may not be able to respond to symptoms promptly)
Hypoglycaemia unawareness
People at high fall and fracture risk

Recurrent hypoglycaemia may be an important impediment to achieving good glycaemic control. Patients who fear hypoglycaemia are unlikely to titrate insulin as instructed, and may also overeat for protection, setting up a vicious cycle of weight gain, hyperglycaemia and increasing insulin doses – the adage of "hypoglycaemia begets hypoglycaemia". Patients receiving hypoglycaemic drugs must be questioned about hypoglycaemia at every visit, in order to address treatment failures. Any patient who has a severe hypoglycaemic event must be evaluated for a cause and must have their treatment reviewed. Any treatment plan should have ready access to drugs that do not cause hypoglycaemia when the circumstances demand this.

d. Weight gain

Weight effects of medications are considered separately because of their importance to patients' quality of life and self-esteem, and treatment compliance. Obesity, as part of the metabolic syndrome, is a well-known cardiovascular risk factor. Weight gain after diagnosis of type 2 diabetes may also be a risk factor for cardiovascular disease but this remains to be proven.[21] Metformin, SGLT2 inhibitors, and GLP-1 agonists are associated with weight loss, DPP-4 inhibitors and acarbose are weight neutral, whereas sulphonylureas cause modest weight gain. Weight gain is worst with pioglitazone and insulin.[9–12]

Patients who experience significant weight gain (as defined by themselves) with pioglitazone or insulin are unlikely to comply with their treatment. They may be better served with a less effective treatment with better compliance. Alternative treatment options should be considered for patients who experience unacceptable weight gain.

e. Adverse effects

Adverse effects other than hypoglycaemia and weight gain, which are considered separately, should be taken into account. Common adverse effects can limit compliance and adherence to therapy. Each patient's potential to tolerate common adverse effects needs to be considered. Metformin has common GI side effects leading to about a 10% discontinuation rate. In the LEAD 6 trial program 15-20% of patients discontinued GLP-1RA therapy. Similarly genitourinary side effects may limit the use of SGLT2 inhibitors. Patients should be warned about the common adverse events when commencing therapy.

f. Serious adverse events

The rare but serious adverse events for each drug/class are discussed individually. SEMDSA has considered the impact these have on patient selection and ease of prescribing in the primary healthcare setting.

g. Treatment complexity

The choice of treatment considers the patient, provider and general healthcare resources that may be required for a particular therapeutic choice. The use of insulin therapy is a good example of treatment complexity. Escalation to insulin therapy is premised on information from clinical trials demonstrating equivalent and sometimes better glycaemic control than other therapeutic options. These trials often exclude patients who are unable or unwilling to perform and record frequent SMBG or to "force-titrate" insulin doses to strict glycaemic targets. These trial patients receive intensive education about insulin use, injection technique, SMBG, titration protocols and are provided with adequate supplies of insulin, needles and test strips. They also have ongoing education, very frequent clinic follow-up visits (usually two to four weeks apart) and continual, unlimited telephonic support. Translating the positive glucose control results from such trials into daily clinical practice in some/most/all primary healthcare centers may sometimes be a "mis-translation". The patient may be given a prescription for one or other insulin, possibly with very little or no ongoing education on how to use it, with no titration instruction or protocol, perhaps a limited supply of test-strips (if at all), and no access to support for months on-end. In this regard insulin therapy could be construed as a "pseudo-escalation" of treatment. Given the relative demands of insulin initiation and titration for the patient and clinic staff, might the patient be better served with a somewhat less efficacious oral glucose lowering drug that has a lower complexity.

Other aspects of treatment complexity to be considered include assessments and counseling before and after a drug prescription in order to ensure patient safety, e.g. assessment of fracture risk for patients being considered for pioglitazone or canagliflozin treatment.

h. Patient factors

The entire point in considering all the features about each pharmacological agent is, of course, to find the "best-fit" for the patient. Each patient has their own needs and fears, and each has their own expectation of treatment outcomes.

11.3 The 2017 SEMDSA approach and algorithm for the management of type 2 diabetes

In planning the treatment algorithm, the SEMDSA Expert Committee was cognisant that the majority of type 2 diabetes patients are, and should be, managed at primary healthcare facilities. There is evidence though, that the standards of care for type 2 diabetes at all levels is not adequate,[22–28] and that interventions to improve processes of care for non-communicable diseases may not be successful.[29] The current local evidence is that 10 to 30% of patients achieve an HbA_{1C} of <7.0% and as many as 30% have an HbA_{1C} > 11%. It is clear that a metformin-sulphonylurea-insulin strategy is not effective in the South African primary health care setting. The purpose of this algorithm therefore is to improve glycaemic control by attempting to give primary healthcare practitioners the tools needed to achieve this in a way that is both safe and effective.

A few caveats about this algorithm need emphasizing. Firstly, it is a guideline for primary healthcare; patients managed at specialist care level often have multiple comorbidities and more severe disease requiring more complex therapies. Secondly, the algorithm applies to the stable type 2 diabetes patient who has suboptimal glycaemic control; it does not apply to the metabolically decompensated patient with severe symptomatic hyperglycaemia; those patients usually need referral for intensive management. Thirdly, it does not apply to patients with severe microvascular or macrovascular complications; these patients should also be managed under specialist supervision, and the optimal treatment options differ from this algorithm. Lastly, this can only serve as a guideline and cannot, and should not be applied rigidly to the very heterogeneous type 2 diabetes population (as discussed above). However, the suggested therapeutic options should cater for the glucose control needs of the majority of type 2 diabetes patients who are being managed appropriately in the primary healthcare setting.

The algorithm should be interpreted in conjunction with the "Pharmacological Management" Chapters 9 and 10, which provide a summary of each drug, as well as with the recommendations for each drug below. For those wanting more detailed information, a review of each drug class is provided in the Appendix. The footnotes explain the algorithm in greater detail.

2017 SEMDSA algorithm for the management of type 2 diabetes in non-pregnant adults without metabolic decompensation or cardiovascular disease

Preferred options are listed alphabetically.

Footnote to the 2017 SEMDSA algorithm for the management of type 2 diabetes

Reinforce advice on diet and lifestyle at every contact.

If the patient has metabolic decompensation (marked weight loss, FPG > 14 mmol/L,HbA_{1C} > 10% or a hyperglycaemic emergency) at diagnosis, or at any stage, consider specialist referral for intensive insulin therapy. Decide on an individualised HbA_{1C} target using the guidelines in Chapter 8. Monitor HbA_{1C} every three months until the target is achieved; then every six months. Always assess the response to added treatments; if the HbA_{1C} reduction is not > 0.5% after 3-6 months, consider treatment failure and change to an alternative option.

Monotherapy

In newly diagnosed patients the target HbA_{1C} should be <6.5% unless there are factors that preclude this. Metformin remains the drug of first choice at diagnosis, and if tolerated, should be continued until contraindicated. If tolerability is poor, consider switching to the extended release formulation. If metformin is contraindicated or not tolerated consider gliclazide MR if the HbA_{1C} target is <7%, or a DPP-4 inhibitor / pioglitazone if the HbA_{1C} target is <6.5%. SGLT2 inhibitors, GLP-1RAs and insulin are not recommended alternatives to metformin; they offer no compelling additional benefits at this stage of the disease to justify the additional cost. Established cardiovascular disease would be a compelling reason to use either an SGLT2 inhibitor or GLP-1RA in metformin intolerant patients (under specialist care).

Consider initial dual therapy with metformin + gliclazide MR if the patient has symptomatic hyperglycaemia and HbA_{1C} is >9% at diagnosis. The decision to continue gliclazide MR can be reviewed when metformin dose and lifestyle interventions have been optimised.

Dual Therapy

If the HbA_{1C} target is not achieved after three months of metformin or subsequently rises, consider adding gliclazide MR, a DPP-4 inhibitor, pioglitazone, or an SGLT2 inhibitor. Revise the HbA_{1C} target if necessary. The HbA_{1C} target for the majority of patients should be <7% (in recently diagnosed patients who have not yet achieved their target it can remain at < 6.5% provided it can still be achieved safely). Consider patient preference, comorbidities, and ability to access medicines as well as the properties of each drug (see Figure I and text recommendations). Consider gliclazide MR for most patients whose target is <7%. If the target is <6.5% or there are other reasons why gliclazide MR cannot be used (e.g. recurrent hypoglycaemia), then consider a DPP-4 inhibitor (or pioglitazone, or an SGLT2 inhibitor) based on the patient profile. Fixed dose combinations of a DPP-4 inhibitor + metformin may have compliance and cost advantages. GLP-1RA and insulin offer no compelling advantages at this stage for the added cost / complexity, provided the HbA_{1C} target is still attainable.

Triple Therapy

If the HbA_{1C} is above the individualised target (which should still be <7% for most patients) with two oral agents, consider adding either a third oral agent or an injectable agent (GLP-1RA or basal insulin) - refer to figure IV. Consider patient preference, comorbidities, and ability to access medicines as well as the properties of each drug (Figure I and text recommendations) in selecting an appropriate option. Do not combine a GLP-1RA with either a DPP-4 inhibitor or an SGLT2 inhibitor, and do not combine pioglitazone with insulin. Expected HbA_{1C} reductions are similar when adding a GLP-1RA or titrated basal insulin, and both are slightly superior to triple oral therapy. Insulin initiation must be accompanied by ongoing patient education, appropriate SMBG, self-titration of insulin doses, frequent review (initially) and counselling regarding hypoglycaemia. In the absence of appropriate support for insulin therapy, a third oral agent is preferred. Use basal insulins with the lowest acquisition cost. Switch NPH to a basal analogue insulin if nocturnal hypoglycaemia is problematic.

Complex Therapy

When triple therapy is inadequate at maintaining or achieving glycaemic targets, combination injectable (complex) therapy will become necessary (refer to figure V). Depending on the support services available, patients at this stage may continue to be managed at primary care level, or be referred for escalation to more complex therapies (including basal-bolus insulin therapy).

For patients on three oral agents, consider escalation to a twice-daily premix insulin regimen with metformin; the other oral agents can be stopped. Alternatively, a DPP-4 inhibitor (if used) may be switched to basal insulin and/or a GLP1RA if the glycaemic target is attainable (basal insulin and GLP1RAs are more efficacious than DPP-4 inhibitors).

For patients already on a single injectable agent (basal insulin or GLP1RA), consider escalation to any of the following 3 options:

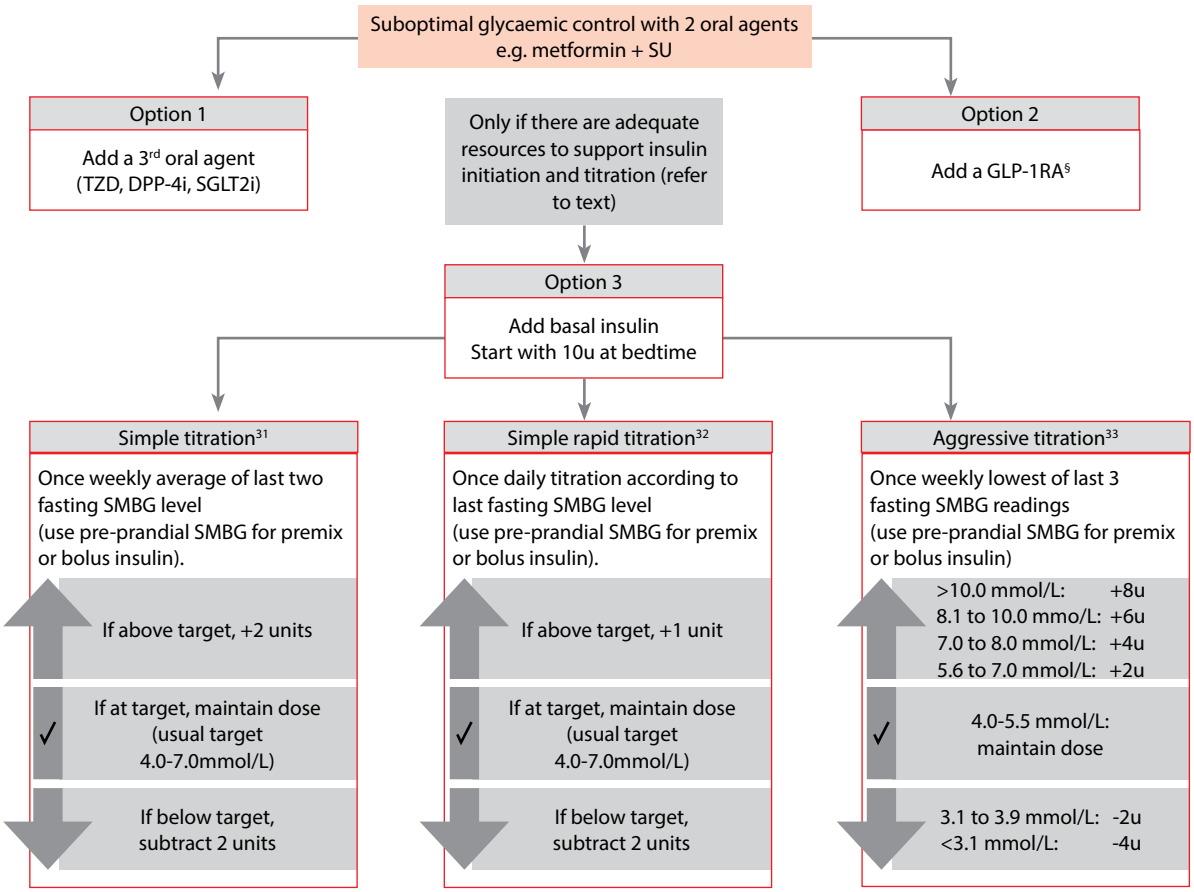
a. Combination basal insulin and GLP-1RA therapy
b. Premix (twice daily) insulin
c. Basal-plus insulin therapy (adding one or more prandial doses of insulin to basal insulin)

Each of these options has advantages and disadvantages that will need to be considered and discussed with the patient. For all three options metformin should be retained; consider stopping the other oral agents to reduce the cost and complexity of the regimen.

Recurrent hypoglycaemia, unacceptable weight gain and treatment failure (failure to achieve an HbA_{1C} level that is within 0.5% of the target, or to lower the HbA_{1C} by more than 1%) with these complex therapies should warrant a critical review of the chosen regimen, and specialist referral.

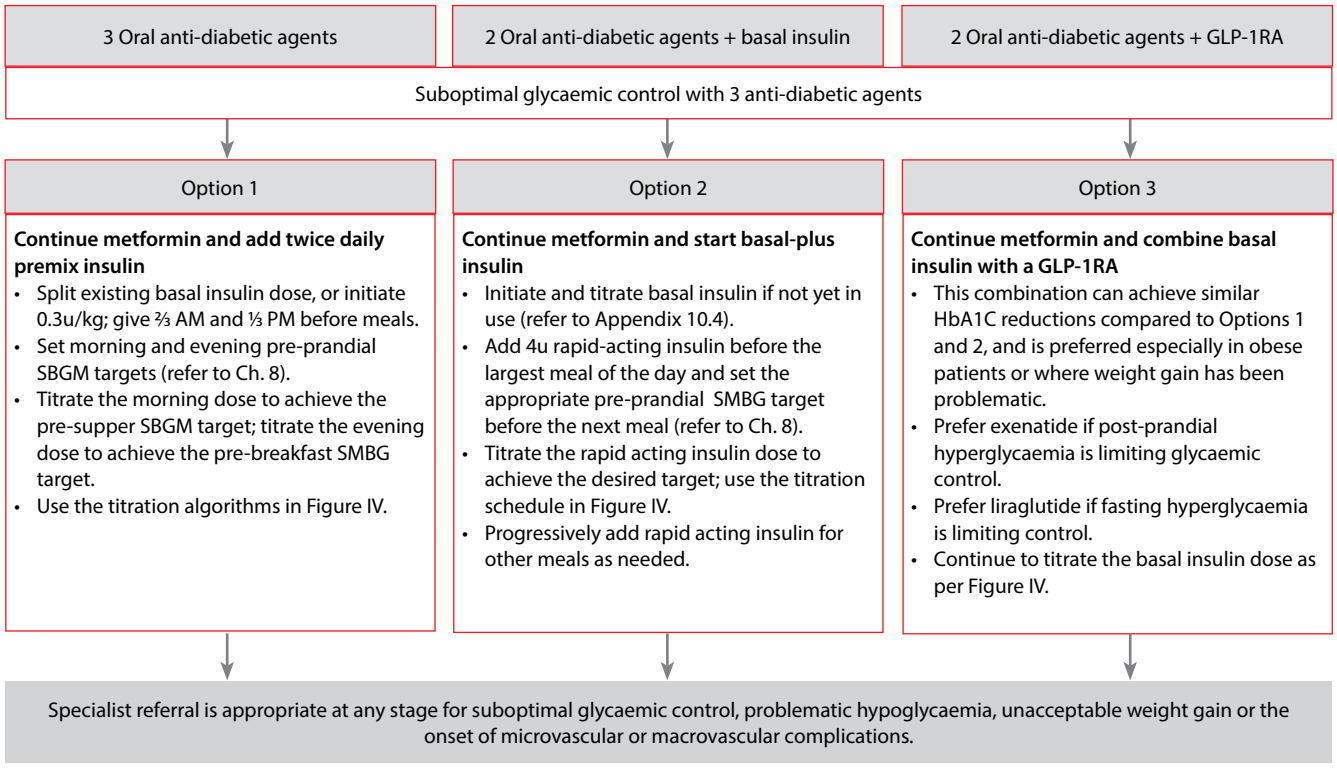
FPG=fasting plasma glucose; gliclazide MR= gliclazide modified release; GLP-1RA=GLP-1 receptor agonist; SMBG=self blood glucose monitoring

Figure IV: Initiating and titrating basal insulin therapy



SU = sulphonylurea; TZD = thiazolidinedione; DPP-4i= DPP-4 inhibitor; SGLT2i = SGLT2 inhibitor; GLP-1RA = GLP-1 receptor agonist; SMBG = self-monitoring of blood glucose
§Do not combine a GLP-1RA with a DPP-4 inhibitor or SGLT2 inhibitor.

Figure V: Complex (combination injection) therapies



GLP-1RA = GLP-1 receptor agonist; SMBG = self- monitoring of blood glucose

11.4 Recommendations for glucose lowering drugs

(Reproduced from Chapter 9)

SEMDSA 2017 Recommendations for metformin

- Initiate standard-release metformin therapy in all newly diagnosed obese patients with type 2 diabetes.
- Initiate standard-release metformin therapy in all newly diagnosed non-obese patients with type 2 diabetes.
- Dosing: Start with 500 mg once daily and up-titrate the dose slowly every 10 to 14 days until glycaemic targets are met or side effects occur. Few patients will achieve and maintain glycaemic targets with 500 mg once daily. Most patients will require1000 – 2550 mg per day in two or three divided doses. The optimum dose for cardiovascular benefit in obese patients is 2550 mg/day (850 mg TDS).
- If gastrointestinal (GI) adverse events are limiting, try temporarily reducing or discontinuing the drug, and re-titrate when the GI disturbances resolve. The GI side-effects with metformin extended-release is not different to the standard release when used as initial therapy; however patients who switch to the extended release may have improved tolerability. If GI disturbances remain intolerable with standard metformin tablets, try switching to a metformin extended release (XR) formulation and titrate the dose every 10-14 days again.
- The extended release formulation should be dosed once daily with the evening meal at a dose not exceeding 2000 mg/day. The 2000 mg dose can be taken as 1000 mg twice a day without disadvantages if the patient so prefers. Patients not achieving their glycaemic target with 2000 mg of the extended release may benefit from switching to a higher dose of the standard release metformin.
- Monitor renal function (eGFR) in all patients at least annually. Do not exceed 1000 mg/day if the eGFR is 30-45 ml/min/1.73m2. Stop metformin therapy if the eGFR is < 30 ml/min/1.73m2
- The significance of low serum vitamin B_{12} levels associated with long-term metformin use is not known. Measure and treat whenever clinically appropriate.
- Profile of the patient in whom metformin may not be the preferred option:
  - Patients with irritable bowel syndrome or other chronic gastrointestinal disorders
  - Normal weight individuals who do not wish to lose weight
  - Patients at high risk for lactic acidosis (severe heart, lung, liver, renal or peripheral vascular disease)
  - There is a history of metformin intolerance.

SEMDSA 2017 Recommendations for sulphonylureas

- The sulphonylurea of choice should be gliclazide modified-release because:
  - It has equivalent efficacy compared to other sulphonylureas.
  - It is consistently associated with lower rates of hypoglycaemia and better cardiovascular and renal safety relative to other sulphonylureas.
  - It has proven benefits for long-term microvascular disease outcomes.
- Glibenclamide must not be used at primary care level.
- Consider gliclazide modified-release as initial monotherapy when metformin is not tolerated or is contraindicated.
- Consider gliclazide modified-release as add-on (dual therapy) to metformin (or other initial drug therapy) in most patients not achieving or maintaining their glycaemic targets.
- If not already in use, consider gliclazide modified-release as a third glucose lowering drug.
- To convert treatment from another sulphonylurea to gliclazide modified-release, use the following dose conversion:
  - Glibenclamide 5 mg ≈ Gliclazide modified-release 30 mg
  - Glimepiride 1-2 mg ≈ Gliclazide modified-release 30 mg
- Only continue gliclazide modified-release beyond stage 3 chronic kidney disease (when the eGFR is less 30 ml/min/m^2) with specialist supervision.
- Circumstances where gliclazide MR may be preferred to other treatment options:
  - Gliclazide MR should be the preferred second drug for the majority of patients with type 2 diabetes.
  - At diagnosis when rapid control of hyperglycaemic symptoms is required.
- Circumstances where gliclazide MR may not be the preferred option:
  - The individualised glycaemic target is ≤ 6.5% (as the risk of hypoglycaemia may be unacceptably high with this target).
  - There is a history of severe hypoglycaemia or hypoglycaemia unawareness.
  - There is a history of recurrent hypoglycaemia (any degree) despite dose adjustments.
  - The risk of hypoglycaemia is high and/or its consequences are severe.
  - The patient has advanced liver disease.

SEMDSA 2017 Recommendations for pioglitazone

- Consider pioglitazone as initial monotherapy when metformin is contraindicated or not tolerated.
- Consider pioglitazone as add-on to metformin or other initial drug therapy, in selected patients not achieving or maintaining their glycaemic targets.
- Consider pioglitazone as a third non-insulin glucose lowering drug in selected patients not achieving or maintaining their glycaemic targets on an existing oral two-drug regimen.
- Circumstances where pioglitazone is preferred to other treatment options:

- Gliclazide MR is contraindicated or not tolerated.
- Non-alcoholic steatohepatitis is present.
- The patient has features of severe insulin resistance.
- There is a history of previous myocardial infarction, previous stroke or chronic kidney disease stage-3 (pioglitazone offers probable benefit for secondary prevention)

- Circumstances where pioglitazone may not be the preferred option:
  - Age > 75 years old (risk of congestive heart failure (CHF), fracture and bladder cancer)
  - History of congestive heart failure.
  - History of osteoporosis.
  - History of bladder cancer, or haematuria that has not been investigated.
  - Stage-4 or worse chronic kidney disease (risk of fluid retention).
  - Patients on insulin therapy (higher risk of fluid retention and CHF).
  - Elevated liver enzymes (>2x ULN) not due to NASH.

SEMDSA 2017 Recommendations for DPP-4 inhibitors

- Consider a DPP-4 inhibitor as initial monotherapy when metformin is contraindicated or not tolerated.
- Consider a DPP-4 inhibitor as add-on to metformin or other initial drug therapy, in selected patients not achieving or maintaining their glycaemic targets.
- Consider a DPP-4 inhibitor as the third glucose lowering drug in selected patients not achieving or maintaining their glycaemic targets on an existing oral two-drug regimen.
- Combination DPP-4 inhibitor and insulin therapy should be initiated at specialist level.
- Be aware of dose adjustments for chronic kidney disease.
- Circumstances where a DPP-4 inhibitor may be preferred to other treatment options:
  - As the 2nd add-on drug when gliclazide MR is contraindicated or not tolerated.
  - As the 3rd add on drug for most patients if HbA_{1C} targets are potentially achievable.
  - Older patients with multiple comorbidities.
  - Patients with stage-4 chronic kidney disease (can be used without risk of hypoglycaemia).
  - If a fixed-dose combination tablet will improve adherence, compliance and/or cost-effectiveness.
- Circumstances where a DPP-4 inhibitor may not be the preferred option:
  - Very high HbA_{1C} and the glycemic target is not likely to be achieved with a DPP-4 inhibitor.
  - History of pancreatitis or pancreatic tumour.
  - History of heart failure or high risk of heart failure (saxagliptin).
  - Liver disease: moderate (do not use saxagliptin or vildagliptin) or severe (do not any DPP-4 inhibitor).

SEMDSA 2017 Recommendations for GLP-1 receptor agonists (GLP-1RA)

- Consider a GLP-1RA injectable as the third glucose lowering drug (triple therapy) in overweight and obese patients when glycaemic targets are not being achieved or maintained.
- Consider adding a GLP-1RA to existing basal insulin therapy (with oral therapies) as an alternative to intensifying the insulin regimen, especially when weight gain and/or hypoglycaemia is a limiting factor.
- Escalate the dose of GLP-1RA slowly to minimise side-effects.
- Circumstances where a GLP-1RA may be preferred to other treatment options:
  - Overweight and obese patients
  - Weight gain or hypoglycaemia has been, or is likely to be problematic with other treatment options.
  - HbA_{1C} is very high (GLP-1RA and insulin are the most effective glucose lowering drugs for most patients).
  - Patients with established cardiovascular disease (liraglutide benefit); to be managed at specialist care level.
- Circumstances where a GLP-1RA may not be the preferred option:
  - Patients in whom weight loss is not desirable.
  - Patients with chronic gastrointestinal disorders.
  - Patients with a history of pancreatitis or pancreatic tumour.

SEMDSA 2017 Recommendations for SGLT2 inhibitors

- Do not use SGLT2 inhibitors as initial monotherapy
- Consider an SGLT2 inhibitor as add-on (dual therapy) to metformin (or other initial drug therapy) in selected patients not achieving or maintaining their glycaemic targets.
- Consider an SGLT2 inhibitor as the 3rd glucose lowering drug in selected patients not achieving or maintaining their glycaemic targets on an existing oral two-drug regimen.
- Circumstances where an SGLT2inhibitor may be preferred to other treatment options:
  - Overweight and obese patients.
  - Weight gain or hypoglycaemia has been, or is likely to be problematic with other treatment options.
  - Patients with established cardiovascular disease (empagliflozin benefit); to be managed at specialist care level.
- Circumstances where an SGLT2 inhibitor may not be the preferred option:
  - Patients with recurrent mycotic genital infections or urinary tract infections.
  - Patients at risk for dehydration and hypotension.
  - Patients at high risk for stroke, fracture (canagliflozin), amputation (canagliflozin), bladder cancer (dapagliflozin) or ketoacidosis (refer to drug review).

- Do not initiate SGLT2 inhibitors when the eGFR is < 60 ml/min/m^2.
- Stop all SGLT2 inhibitors when the eGFR is < 45 ml/min/m^2.

Author: Aslam Amod

Editors: Zaheer Bayat, Ankia Coetzee, Nazeer A Mohamed, Joel A Dave, Tanya Kinvig and Fraser J Pirie

References

1. Shisana O, Labadarios D, Rehle T, et al. South African National Health and Nutrition Examination Survey, 2012 (SANHANES-1). In: 2014th ed. Cape Town: HSRC Press; 2014:1-397.
2. Bonora E, Targher G, Alberiche M, et al. Predictors of insulin sensitivity in Type 2 diabetes mellitus. Diabet Med. 2002;19(7):535-542.
3. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364-1379. doi:10.2337/dc12-0413.
4. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38(1):140-149. doi:10.2337/dc14-2441.
5. Harper W, Clement M, Goldenberg R, et al. Pharmacologic Management of Type 2 Diabetes. Can J Diabetes. 2013;37:S61-S68. doi:10.1016/j.jcjd.2013.01.021.
6. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association Of Clinical Endocrinologists And American College Of Endocrinology – Clinical Practice Guidelines For Developing A Diabetes Mellitus Comprehensive Care Plan – 2015 — Executive Summary. Endocr Pract. 2015;21(4):413-437. doi:10.4158/EP15672.GL.
7. American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment. Sec. 8. In Standards of Medical Care in Diabetes 2017. Diabetes Care. 2017;40(Supplement 1):S64-S74. doi:10.2337/dc17-S011.
8. Holman RR, Thorne KI, Farmer AJ, et al. Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. N Engl J Med. 2007;357(17):1716-1730. doi:10.1056/NEJMoa075392.
9. Liu S-C, Tu Y-K, Chien M-N, Chien K-L. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. Diabetes, Obes Metab. 2012;14(9):810-820. doi:10.1111/j.1463-1326.2012.01606.x.
10. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes. JAMA. 2016;316(3):313. doi:10.1001/jama.2016.9400.
11. Bennett WL, Maruthur NM, Singh S, et al. Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations. Ann Intern Med. 2011;154(9):602. doi:10.7326/0003-4819-154-9-201105030-00336.
12. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The Effect of Oral Antidiabetic Agents on A1C Levels: A systematic review and meta-analysis. Diabetes Care. 2010;33(8):1859-1864. doi:10.2337/dc09-1727.
13. European Medicines Agency. Jardiance : European Public Assessment Report - Product Information. Updated 07 December 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002677/WC500168592.pdf. Accessed February 10, 2016.
14. Bedenis R, Price AH, Robertson CM, et al. Association Between Severe Hypoglycemia, Adverse Macrovascular Events, and Inflammation in the Edinburgh Type 2 Diabetes Study. Diabetes Care. 2014;37(12):3301-3308. doi:10.2337/dc14-0908.
15. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased Mortality of Patients With Diabetes Reporting Severe Hypoglycemia. Diabetes Care. 2012;35(9):1897-1901. doi:10.2337/dc11-2054.
16. Mellbin LG, Ryden L, Riddle MC, et al. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J. 2013;34(40):3137-3144. doi:10.1093/eurheartj/eht332.
17. Zoungas S, Patel A, Chalmers J, et al. Severe Hypoglycemia and Risks of Vascular Events and Death. N Engl J Med. 2010;363(15):1410-1418. doi:10.1056/NEJMoa1003795.
18. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ. 2013;347(jul29 3):f4533-f4533. doi:10.1136/bmj.f4533.
19. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010;340(jan08 1):b4909-b4909. doi:10.1136/bmj.b4909.
20. Clayton D, Woo V, Yale J-F. Hypoglycemia. Can J Diabetes. 2013;37:S69-S71. doi:10.1016/j.jcjd.2013.01.022.
21. Bodegard J, Sundström J, Svennblad B, Östgren CJ, Nilsson PM, Johansson G. Changes in body mass index following newly diagnosed type 2 diabetes and risk of cardiovascular mortality: A cohort study of 8486 primary-care patients. Diabetes Metab. 2013;39(4):306-313. doi:10.1016/j.diabet.2013.05.004.
22. Erasmus RT, Blanco Blanco E, Okesina a B, Gqweta Z, Matsha T. Assessment of glycaemic control in stable type 2 black South African diabetics attending a peri-urban clinic. Postgrad Med J. 1999;75(888):603-606.
23. Pinchevsky Y, Shukla V, Butkow N, Raal FJ, Chirwa T. The achievement of glycaemic, blood pressure and LDL cholesterol targets in patients with type 2 diabetes attending a South African tertiary hospital outpatient clinic. J Endocrinol Metab Diabetes South Africa. 2015;20(2):28-34. doi:10.1080/16089677.2015.1056468.
24. Pinchevsky Y, Butkow N, Raal F, Chirwa T. The implementation of guidelines in a South African population with type 2 diabetes. J Endocrinol Metab Diabetes South Africa. 2014;18(3):154-158. doi:10.1080/22201009.2013.10872322.
25. Pillay S, Sa FCP, Physician S, Aldous C, Lecturer S. Diabetic patients served at a regional level hospital : what is their clinical picture ? J Endocrinol Metab Diabetes South Africa. 2015;20(1):60-66.
26. Steyn K, Levitt NS, Patel M, Gwebushe N, Lombard C, Everett K. Hypertension and diabetes: Poor care for patients at community health centres. J Endocrinol Metab Diabetes South Africa. 2008;13(2):64-70. doi:10.1080/22201009.2008.10872172.
27. Igbojiaku OJ, Harbor OC, Ross A. Compliance with diabetes guidelines at a regional hospital in KwaZulu-Natal, South Africa. African J Prim Heal Care Fam Med. 2013;5(1):1-5. doi:10.4102/phcfm.v5i1.447.
28. Amod A, Riback W, Schoeman HS. Diabetes guidelines and clinical practice: is there a gap? The South African cohort of the International Diabetes Management Practices Study. J Endocrinol Metab Diabetes South Africa. 2012;17(2):85-90.
29. Steyn K, Lombard C, Nomonde Gwebushe, et al. Implementation of national guidelines, incorporated within structured diabetes and hypertension records at primary level care in Cape Town, South Africa: A randomised controlled trial. Glob Health Action. 2013;6(1). doi:10.3402/gha.v6i0.20796.
30. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999;281(21):2005-2012.
31. Endocrinologic and Metabolic Drug Advisory Committee. Insulin degludec and insulin degludec/insulin aspart treatment to improve glycaemic control in patients with diabetes mellitus: NDAs 203314 and 203313 FDA briefing document. Published November 8,2012
32. Type-2 diabetes insulin initiation & titration suggestions: Insulin prescription [Internet]. Toronto: Ontario College of Family Physicians; 2007. [Accessed 20 Feb 2016]. Available from: http://www.ocfp.on.ca/English/OCFP/Communications/CurrentIssues/Insulin/default.asp?s=1
33. Adapted from: Riddle MC, Rosenstock J, Gerich J. The Treat-to-Target Trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003;26(11):3080-3086. doi:10.2337/diacare.26.11.3080.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Chapter 12: Hypoglycaemia in type 2 diabetes

SEMDSA Type 2 Diabetes Guideline Expert Committee

SEMDSA 2017 Recommendations	
In diabetes patients using insulin and insulin secretagogues (sulphonylureas and meglitinides), hypoglycaemia is an important limitation to achieving optimal glycaemic control in individuals with diabetes	A
Hypoglycaemia is defined as per the International Hypoglycaemia Study Group according to self-monitored blood glucose (SMBG) or continuous glucose monitoring (CGM) values: ◦ The glucose alert value for hypoglycaemia is less than 3.9 mmol/L ◦ Significant hypoglycaemia is a blood glucose value less than 3.0 mmol/L ◦ Severe hypoglycaemia is any low blood glucose value that is accompanied by cognitive dysfunction and a need for external assistance to correct the hypoglycaemia.	C
Identify patients at high risk of hypoglycaemia; they include patients using insulin and/or insulin secretagogues, those on multiple glucose lowering drugs, the elderly, those with renal, hepatic or cognitive impairment, patients who exercise or skip meals and those with excessive alcohol intake.	A
Educate patients using insulin and/or secretagogues to be prepared for unexpected hypoglycaemia, to identify the symptoms of hypoglycaemia, to confirm the hypoglycaemia with SMBG whenever possible, and to correct the hypoglycaemia quickly; advise them that oral glucose (15-20g) is the preferred treatment for non-severe hypoglycaemia and offer them advice on alternative glucose sources.	C
Use intravenous 50% dextrose water to correct severe hypoglycaemia; use 1mg subcutaneous or intra-muscular glucagon if there is no intravenous access.	C
Severe hypoglycaemia is a strong associated risk factor for cardiovascular morbidity and mortality especially in people with pre-existing cardiovascular disease, and should be avoided by adjusting treatment or glycaemic targets.	B
Individuals at risk for severe hypoglycaemia (e.g. those with a previous significant or severe hypoglycaemic episode, hypoglycaemia unawareness, cognitive impairment) must have a prescription for a glucagon kit; ensure adequate training of caregivers on how to store and use the glucagon kit.	C
Attempt to establish the cause of each hypoglycaemic episode and take appropriate remedial action. Any episode of severe hypoglycaemia or hypoglycaemia unawareness must prompt a re-evaluation of the treatment regimen. Patients with recurrent severe hypoglycaemia and/or hypoglycaemia unawareness should be referred to an endocrinologist.	C
Continuous glucose monitoring (CGM) can be used to evaluate patients with recurrent hypoglycaemic episodes and those with hypoglycaemic unawareness.	B

12.1 Definitions

Hypoglycaemia in *non-diabetic* individuals is defined clinically by Whipple's triad: symptoms of hypoglycaemia, a plasma glucose concentration < 3.0 mmol/l, and resolution of those symptoms after the plasma glucose concentration is raised.[1] The symptoms are due to sympathoadrenergic activation (autonomic) and neuroglycopaenia, the symptoms of which are listed in Table I.

In diabetes a single glucose value cannot be used to define hypoglycaemia based on the onset of symptoms because

Table I: Symptoms and signs of hypoglycaemia

Autonomic	Neuroglycopaenic
Sweating	Poor concentration
Warmth	Drowsiness / dizziness
Anxiety	Confusion
Tremor	Weakness
Nausea	Visual disturbances
Palpitations	Speech abnormalities
Tachycardia	Headache
Hunger	Seizures
	Coma

Table II: Classification of hypoglycaemia[3]

Level	Glucose criteria (SMBG)	Description
Glucose alert value (Level 1)	Less than 3.9 mmol/L	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (Level 2)	Less than 3.0 mmol/L	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (Level 3)	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

the blood glucose level at which symptoms start varies in the same patient and between patients, depending on preceding glycaemic control; individuals with recurrent recent hypoglycaemia may only experience symptoms at much lower blood glucose levels (<3 mmol/L), and those with recent marked hyperglycaemia can have symptoms at blood glucose levels in the normal range (relative hypoglycaemia).[2] The American Diabetes Association (ADA) therefore defines ***diabetic hypoglycaemia*** as "all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm" without specifying a numerical value.

However, the ADA and other groups also identified the need for a blood glucose value that draws the attention of both patients and caregivers to the harm associated with potentially impending hypoglycaemia. This ***glucose alert value*** has been defined as a self-monitored blood glucose (SMBG) less than 3.9 mmol/L for patients receiving treatment with insulin and/or insulin secretagogues.[2,3] ***Clinically significant hypoglycaemia*** is defined by blood glucose <3.0 mmol/L. ***Severe hypoglycaemia*** is any low blood glucose associated with cognitive impairment and requiring external assistance for recovery.[3] (Table II)

12.2 Clinical Implications of hypoglycaemia

Hypoglycaemia is a common problem which is an important limitation to achieving optimal glycaemic control in individuals with diabetes who are treated with insulin and/or insulin secretagogues (viz. sulphonylureas and meglitinides). The short-term implications range from unpleasant symptoms to severe cognitive impairment with the potential to cause harm to the individual with diabetes as well as to others. These episodes may result in falls, motor vehicle accidents or other injuries.[4] Prolonged severe hypoglycaemia can cause transient neurological deficits such as paralysis, seizures, and coma. It may cause permanent neurological damage or brain death, and may be responsible for sudden death (the "dead in bed syndrome").

Potential long-term effects include reduced quality of life, fear of hypoglycaemia (which will impact glycaemic control) and weight gain. Hypoglycaemia has been associated with a greater risk of dementia:[5,6] However, it is not clear whether this is cause or effect.

Clinicians should be aware of relative hypoglycaemia and patients should be encouraged to monitor their fingerprick glucose whenever they develop symptoms suggestive of hypoglycaemia. Hypoglycaemic episodes can occur in the setting of patients with elevated HbA_{1c} levels making glucometer download of readings an important component of each consultation with a diabetic patient. Lipohypertrophy can result in erratic glucose readings, including hypoglycaemia. Therefore, all patients on insulin should have their injection sites inspected at each consultation.

12.2.1 Severe hypoglycaemia and cardiovascular disease

Cardiovascular disease is a major cause of mortality in type 2 diabetes and a reduction in cardiovascular outcomes has been the focus in 3 large glucose-lowering trials viz. ACCORD, ADVANCE, and VADT.[7–9] Not only did these studies not demonstrate any cardiovascular benefit, but the ACCORD study had to be prematurely halted because of an increased mortality in the intensively treated arm as compared to the standard arm. Although the rates of severe hypoglycaemia were higher in patients who were treated with intensive therapy, several *post hoc* analyses have failed to determine the underlying cause of the higher mortality associated with strict glycaemic control.[10–13]

Irrespective of whether severe hypoglycaemia is causal or a consequence of vulnerability, it remains a strong predictor of cardiovascular morbidity and mortality and should be avoided. It is acknowledged that the consequences of hypoglycaemia are greatest in those with severe hypoglycaemia, the frail, and those with pre-existing cardiovascular disease.[13]

Putative mechanisms by which hypoglycaemia may increase cardiovascular disease and death, if it is indeed causal, include inflammation, endothelial dysfunction, blood coagulation abnormalities and an increased sympathoadrenal response causing haemodynamic changes and cardiac rhythm abnormalities.[14]

12.3 Risk factors for hypoglycaemia in the diabetic patient

These include:

- Exercise (common)
- Decreased food intake (common): missed or late meals, or small meals
- Inappropriate insulin or insulin secretagogue use/dose
- Intensive treatment with combination therapy
- Renal impairment
- Alcohol intake
- Lower cognitive function.

12.4 Management

In the long-term, management should be aimed at preventing or decreasing the frequency and severity of hypoglycaemic episodes in those who are at risk such as the elderly.

12.4.1 Management of non-severe hypoglycaemia

Patients should be advised to check their SMBG level at the onset of hypoglycaemic symptoms, as this will avoid erroneous rapid correction of relative hypoglycaemia in those with hyperglycaemia / poor glycaemic control. SMBG confirmation, while preferable, should not delay corrective action.

Patients who do not have hypoglycaemia unawareness should be able to correct the condition independently, quickly and early by ingesting 15 – 20 g glucose. This is equivalent to:

1. 15-20 g of glucose powder or glucose tablets
2. 3 to 4 teaspoons of sugar /sucrose (glucose + fructose) dissolved with a little water.
3. ¾ cup or ½ a can (175 ml) of fruit juice or soft-drink
4. 6 to 8 Lifesavers or 2 to 3 Super-C sweets
5. 1 to 1½ tablespoons (15 to 20 ml) of honey

If necessary, this step should be repeated within 10-15 minutes. Thereafter, slowly digestible carbohydrates (e.g. bread) and protein (e.g. milk) must be taken for prolonged restoration of the blood glucose. Patients using insulin and/or insulin secretagogues should always carry glucose or sucrose for emergencies in their pockets / handbags / cars.

12.4.2 Management of severe hypoglycaemia

The patient should be treated immediately. Once the patient has recovered, he or she should be admitted to hospital.

The following steps should be taken on presentation of a suspected hypoglycaemic patient:

1. Establish a large-bore intravenous (IV) line.
2. Administer an immediate, rapid IV injection of 20 - 50 ml of 50% dextrose solution.
3. Assess the clinical and biochemical response over the next 5-10 minutes. If the blood glucose remains < 4.4 mmol/l, give a second IV injection of 20 - 50 ml 50% dextrose.
4. Continue the IV infusion of 10% dextrose in water, at a rate of about one litre over six hours, to prevent recurrent hypoglycaemia, particularly if induced by long-acting insulin and/or a sulphonylurea. For patients that are alcoholic or malnourished, continue the IV infusion with 5% dextrose in water plus thiamine100 mg intramuscular (IM) injection.
5. Once blood glucose is normal or has been elevated and the patient is awake, provide him or her with a snack.
6. If IV dextrose cannot be administered for any reason, inject 1 mg glucagon IM or subcutaneously. The blood glucose will take 10-15 minutes to rise. Importantly, glucagon should not be used in sulphonylurea-induced hypoglycaemia, as it may worsen the condition by further stimulating insulin release.
7. If the patient has not regained consciousness after 30 minutes, despite normal or elevated blood glucose level, other causes of coma will need to be considered (e.g. meningitis). Urgent referral to a specialist is indicated.
8. Refer all patients with severe hypoglycaemia to hospital for observation and education to prevent further hypoglycaemic episodes.
9. In hospital, monitor the clinical state and blood glucose four-hourly for 24-48 hours.
10. Always try to identify the underlying cause of the hypoglycaemic episode.

Glucagon kits (GlucaGen HypoKit®)

A glucagon emergency kit should be available in all emergency rooms. In addition, patients who experience recurrent severe hypoglycaemia, those at very high risk for hypoglycaemia and those who are hypoglycaemia unaware should be given one of these kits for home use. Family members will need to be trained to reconstitute the powder and solvent, and can be taught to safely administer glucagon by subcutaneous or intramuscular injection when oral glucose cannot be administered. Warn patients to always check that the glucagon kit is not expired.

Some important points to consider:

If hypoglycaemia was caused by a sulphonylurea drug, the patient may need hospitalisation and IV dextrose or glucose infusion for several days, particularly if glibenclamide was the cause or renal impairment is present.

Honey or glucose syrup can be rubbed on the gums of patients who have lost consciousness if other medication is not readily at hand.

12.5 Education

It is essential that the cause of each hypoglycaemic episode is established, and appropriate action is taken to prevent further episodes. All diabetic patients must be given education on the recognition and treatment of hypoglycaemia.

12.6 Recurrent hypoglycaemia

All patients with recurrent hypoglycaemia should be referred to a specialist facility for assessment.

Consider the following in cases of recurrent hypoglycaemia:

- Inappropriate management
- Poor adherence to treatment
- Alcohol abuse
- Self-induced hypoglycaemia
- Renal impairment / failure
- Hypoglycaemia unawareness
- Drug interactions / herbal toxins
- Liver disease
- Non-diabetic causes of hypoglycaemia e.g. insulinoma.

12.7 Hypoglycaemia unawareness

This complication occurs after recurrent episodes of hypoglycaemia, and is associated with hypoglycaemia-associated autonomic failure. These patients do not exhibit

the early (autonomic) symptoms of hypoglycaemia, and consequently present with neuroglycopaenia (i.e. confusion, seizures, and coma). Recurrent hypoglycaemia may be the cause or consequence of hypoglycaemic unawareness. Evidence exists that, in some of these individuals, scrupulous avoidance of hypoglycaemia for several weeks may reverse hypoglycaemic unawareness. Patients with hypoglycaemia unawareness should be referred to an endocrinologist and advised to raise their glycaemic targets to strictly avoid hypoglycaemia for at least several weeks. Continuous glucose monitoring is useful in monitoring and managing these patients.

Authors: Nasrin G Mahyoodeen and Kenneth RL Huddle
Editors: Aslam Amod and Joel A Dave

References

1. Desimone ME, Weinstock RS. Non-Diabetic Hypoglycemia. MDText.com, Inc.; 2000.
2. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. J Clin Endocrinol Metab. 2013;98(5):1845-1859. doi:10.1210/jc.2012-4127.
3. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes: Table 1. Diabetes Care. 2017;40(1):155-157. doi:10.2337/dc16-2215.
4. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. Nat Rev Endocrinol. 2014;10(12):711-722. doi:10.1038/nrendo.2014.170.
5. Whitmer RA. Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus. JAMA. 2009;301(15):1565. doi:10.1001/jama.2009.460.
6. Lin C-H, Sheu WH-H. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. J Intern Med. 2013;273(1):102-110. doi:10.1111/joim.12000.
7. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of Intensive Glucose Lowering in Type 2 Diabetes. N Engl J Med. 2008;358(24):2545-2559. doi:10.1056/NEJMoa0802743.
8. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2008;358(24):2560-2572. doi:10.1056/NEJMoa0802987.
9. Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. N Engl J Med. 2009;360(2):129-139. doi:10.1056/NEJMoa0808431.
10. Saremi A, Bahn GD, Reaven PD. A link between hypoglycemia and progression of atherosclerosis in the Veterans Affairs Diabetes Trial (VADT). Diabetes Care. 2016;39(3):448-454. doi:10.2337/dc15-2107.
11. Zoungas S, Patel A, Chalmers J, et al. Severe Hypoglycemia and Risks of Vascular Events and Death. N Engl J Med. 2010;363(15):1410-1418. doi:10.1056/NEJMoa1003795.
12. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010;340(jan08 1):b4909-b4909. doi:10.1136/bmj.b4909.
13. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology. Diabetes Care. 2009;32(1):187-192. doi:10.2337/dc08-9026.
14. Desouza C V., Bolli GB, Fonseca V. Hypoglycemia, Diabetes, and Cardiovascular Events. Diabetes Care. 2010;33(6):1389-1394. doi:10.2337/dc09-2082.

Further reading

Cryer PE, Axelrod L, Grosman AB, et al; Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2009;94:709-728.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 13: Hyperglycaemic emergencies

SEMDSA 2017 Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Blood beta-hydroxybutyrate is the preferred test for the diagnosis and monitoring of diabetic ketoacidosis.	B
Hyperglycaemic emergencies should ideally be managed in a high-care/ICU setting with standardised protocols for management and monitoring.	C
A protocol that incorporates the following principles should be followed: ◦ fluid resuscitation ◦ avoidance of hypokalemia ◦ insulin administration ◦ avoidance of rapidly falling serum osmolality ◦ search for precipitating cause.	C
Administration of sodium bicarbonate in patients with a pH > 6.9 is not recommended.	B
The insulin infusion rate must be maintained, even when blood glucose has normalised, until DKA has resolved. Avoid hypoglycaemia by changing the IV fluid to dextrose when the plasma glucose is ≤ 14 mmol/L.	B
Urinary ketones alone should not be used to confirm the resolution of DKA as this can be misleading. Use a combination of clinical and biochemical measurements to confirm resolution instead.	B
When transitioning to subcutaneous insulin, care must be taken to overlap this with insulin infusion.	B

The hyperglycaemic emergencies, diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS), should be suspected whenever patients have hyperglycaemia, especially if they are systemically unwell or are known to have diabetes. These conditions have significant morbidity and mortality, and emergency treatment with intravenous fluids and insulin is essential.

13.1 The hyperglycaemic emergencies

13.1.1 Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is characterised by uncontrolled hyperglycaemia, high anion gap metabolic acidosis and increased total body ketones. In South Africa, DKA carries a higher mortality than in the developed world. It can present at any age, although it is more common in young patients. It is important to note that urine ketone measurement is not reliable in the diagnosis of DKA.[1] Urinary ketones are commonly detected during fasting, exercise or pregnancy even in the absence of any metabolic derangements. In DKA, the two main ketones produced are acetoacetate (AcAc) and betahydroxybutyrate (BOHB). Urinary dipstix only measures one of these ketone bodies and is also associated with false positive results.[2] BOHB can be measured by lab or validated point of care testing (POCT) device. POCT lends itself ideally for use in the primary health care setting. Uncontrolled hyperglycaemia in the presence of a BOHB level of >3.0 mmol/L indicates unequivocal DKA, whereas a level of <1 mmol/L excludes ketosis.[3]

The diagnosis of DKA can be made on the following criteria:

1. Hyperglycaemia - plasma glucose prior to insulin administration > 13.9 mmol/l
2. Acidosis - indicated by blood pH < 7.3 or bicarbonate below 18 mmol/litre
3. Ketonaemia - indicated by blood beta-hydroxybutyrate > 3 mmol/litre.

13.1.2 Hyperglycaemic hyperosmolar state

The hyperglycaemic hyperosmolar state (HHS) is characterised by the slow development of marked hyperglycaemia (usually > 50 mmol/l), hyperosmolality and severe dehydration. Ketonuria may be slight or absent. The condition usually affects middle-aged or older patients and carries a high mortality. The initial treatment is the same as for DKA.

13.2 Precipitating factors

The clinician should attempt to identify the precipitating factor for DKA once resuscitation has been initiated. The most common precipitating factor is infection. Other precipitants include discontinuation of insulin, myocardial infarction and cerebrovascular accident. In elderly patients, restricted water intake can lead to dehydration and precipitate HHS. Drugs such as diuretics may exacerbate this. Note that a hyperglycaemic crisis can be the presenting feature of both type 1 and type 2 diabetes (e.g. ketosis prone diabetes). In a significant proportion of patients, no precipitant can be identified.

13.3 Clinical features

DKA usually develops acutely (within days), whereas HHS usually evolves over a longer time period (several days to weeks). For both DKA and HHS, the classical clinical picture includes a history of polyuria, polydipsia, vomiting, dehydration, weight loss, weakness and change in mental status. This can vary from mild confusion to profound lethargy or coma, with the latter being more common in HHS. Focal neurological signs and seizures may occur in HHS but the presence of this should always alert the clinician to a possible underlying condition rather than attributing it to the metabolic derangement. Patients with DKA may complain of diffuse abdominal pain even in the absence of primary abdominal pathology. Physical findings may include Kussmaul breathing, and/or features of hypovolemic shock. History taking and examination should not delay the initial management and investigations. Rapid treatment is essential. Once initial resuscitation has been established the patient should be managed at an institution experienced in the management of these conditions, ideally in a high care setting. Table I provides a summary of the characteristics of DKA and HHS, to aid with the recognition of these conditions.

13.4 Treatment of hyperglycaemic emergencies at primary-care level

Rapid treatment is essential and should not be delayed.

The following steps should be followed when treating hyperglycaemic emergencies in the primary-care setting:

- Confirm the diagnosis and initiate management as per algorithm provided.
- Intravenous (IV) fluids:
- IV fluid administration should ideally start with normal saline but if not available can be achieved with other isotonic solutions.[4] In a young patient with suspected DKA, infuse one litre of normal saline over the first hour. In older patients, change fluid to half normal saline after the first litre.
- Administer hourly boluses of ten (10) units of regular insulin IV, until the patient is transferred to hospital. If IV access is problematic, insulin can be given intramuscularly (IM) or subcutaneously (SC) in the interim.[5,6,7,8]
- Arrange transfer to a hospital experienced in the management of hyperglycaemic emergencies.
- Clear instruction should be provided for the continued management during transport.

13.5 Management of hyperglycaemic emergencies in hospital

Refer to Appendix 13a and 13b for a suggested management algorithm and monitoring protocol.

13.5.1 General

- Patients should be managed in a high care/ICU setting, but management should not be delayed until a high care bed is available.
- Mild DKA has been managed in an outpatient setting by means of insulin.[9,10] This is not recommended as the South African primary health care context differs markedly from those where this practice is accepted.
- A thorough investigation for precipitating factors such as infective processes (usually urinary tract and skin) and myocardial ischaemia etc. should be undertaken.
- If infection is suspected antibiotics should be initiated. The choice of antibiotics and continued use thereof should be based on the accepted antibiotic guidelines of the specific institution.
- Should there be delay in the resolution of DKA (usually resolves < 48 hours) a meticulous search for occult infections should be undertaken. This includes otitis media and externa, rhino-cerebral mucormycosis, occult abscesses, pyelonephritis, cholecystitis, osteomyelitis and tuberculosis.
- Prompt surgical intervention should not be delayed even in the presence of metabolic derangements.
- An elevated white cell count should not be over-interpreted as this may occur solely on the basis of DKA.
- Prophylactic antithrombotic treatment is essential.

Table I. Differentiation between the different types of hyperglycaemic coma

	DIABETIC KETO-ACIDOSIS (DKA)	HYPERGLYCAEMIC HYPEROSMOLAR COMA (HHS)
History	Known T1DM Newly-diagnosed DM	Known T2DM Newly-diagnosed DM
Precipitants	Infection, non-compliance on insulin	Infection, MI, CVA, diuretic use contribute to dehydration.
Age frequency	Younger patients	Usually older persons
Onset	Hours to days	Days to weeks
Symptoms	Polyuria, polydipsia, anorexia, nausea, vomiting, abdominal pain	Polyuria, polydipsia, increasing somnolence
Signs	Kussmaul respiration –deep sighing breathing, dehydration, confusion, nausea, vomiting	Severe dehydration, mental status changes, focal neurological signs and/or seizures*.
Urine ketones	Strongly positive	Positive or negative
Serum ketones	Strongly positive	Negative or only weakly positive
Blood glucose	Raised	Markedly raised
Blood pH	Decreased	Normal or slightly decreased
Serum bicarbonate	Low	Normal or slightly decreased

* Exclude underlying pathology.

- Aspiration must be anticipated and prevented. Insert a nasogastric tube if the patient is comatose or has gastric dilatation.
- Frequent reassessment of the patient's condition is necessary. The responsible doctor must keep a meticulous flow chart of the hourly recordings of clinical and biochemical progress and treatment.
- The rate of insulin infusion needs to be adjusted hourly until the expected rate of decline in blood glucose is achieved.

13.5.2 Investigations

The following special investigations should ideally be performed:

Blood tests:

- Glucose, urea and electrolytes (calculate the anion gap), full blood count and differential, and glycated haemoglobin (HbA_{1C})
- Venous blood gas
- Validated plasma, serum or capillary betahydroxybutyrate (BOHB).

Urine tests:

- Dipstick test for nitrites, blood and protein
- Microscopy, culture and sensitivity, if indicated

Chest X-ray

ECG

Other investigations, as appropriate, to investigate for the precipitant of the hyperglycaemic emergency (e.g. blood cultures, sputum culture, cardiac enzymes). Table II provides a list of the laboratory findings which are expected in hyperglycaemic emergencies.

13.5.3 Treatment

13.5.3.1 Intravenous fluids

- DKA: The average fluid deficit in an adult presenting with DKA is 5-10 litres. Patients should receive 1-1.5 litres of fluid in the first hour,[11] and thereafter 250-500ml per hour. The aim is to replace 50% of the fluid deficit during the first 12 hours after presentation, and the remainder within the next 12-16 hours.[12] Normal saline or Ringer's lactate are good choices for initial fluid resuscitation. Hyperglycaemia is corrected faster than ketoacidosis,[11] and 5% dextrose solution should be used once the glucose falls to < 14 mmol/l to prevent hypoglycaemia. If hyperchloraemic (normal anion gap) acidosis occurs in the recovery phase of DKA, minimise hyperchloraemia by using 0.45% saline or 5% dextrose water.
- HHS: If there is no cardiac compromise, the patient can be given one litre of normal saline in the first hour. The subsequent choice of fluid replacement and rate of infusion depends on serum sodium, state of hydration and urinary output. If the corrected serum sodium is normal or high, 0.45% saline infused at 250–500 ml/hour is appropriate. In patients with renal or cardiac compromise, frequent monitoring of serum electrolytes, central venous pressure and urine output is necessary to avoid fluid overload. The fluid replacement guideline is specific to adult patients. Please refer to paediatric guidelines for patients younger than 18 years. Paediatric patients are at increased risk of cerebral oedema if they are fluid overloaded.

13.5.3.2 Insulin

Intravenous short or rapid acting insulin is preferred for the treatment of hyperglycaemic emergencies. Serum potassium should always be checked before insulin infusion.

Continuous insulin infusion at a rate of 0,14 units/kg/hour in a high care or ICU setting with intensive glucose monitoring is the standard of care for the management of DKA.[11] However, treatment of DKA should not be delayed when ICU is not available. It is not advisable to use an insulin infusion outside of ICU or high-care due to the higher risk of hypoglycaemia. Other insulin regimens (IM or IV boluses of 10 units of regular insulin hourly[13] as per institution protocol) may be used if the patient is nursed in the general ward. In either case, capillary glucose should be measured hourly to detect and prevent hypoglycaemia and to assist guiding the rate of insulin infusion. The insulin infusion should be titrated hourly (per institution protocol) in order to address the degree of hyperglycaemia appropriately and to prevent hypoglycaemia.

The switch to subcutaneous insulin can only be made when the hyperglycaemic emergency has resolved:

Table II. Laboratory findings in hyperglycaemic emergencies

	Diabetic Ketoacidosis (DKA)			Hyperglycaemic Hyperosmolar Coma (HHS)
	Mild	Moderate	Severe	
Plasma glucose mmol//	> 13.9	> 13.9	> 13.9	> 33.3
Serum HCO_3 mmol//	15 - 18	10 - 14	< 10	>18
Serum ketones	Positive	Positive	Positive	May be present
Anion gap	>10	>10	>12	Variable
Blood pH	7.25 – 7.30	7.00 – 7.24	< 7.00	> 7.30
Serum osmolality	Variable	Variable	Variable	> 320
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Anion gap = $Na^+ - (Cl^- + HCO3^-)$
Osmolality = $2(Na^+ + K^+)$ + urea + glucose

- The patient is fully conscious and eating
- Anion gap normalised, acidosis resolved (pH > 7.3 Bicarbonate > 18 mmol/l)
- Blood glucose < 15 mmol/l
- BOHB < 1 mmol/l.

13.5.3.3 Potassium

Withhold potassium initially if the ECG and/or serum potassium level reveal marked hyperkalaemia. Start potassium therapy immediately if serum potassium is normal or low and/or the ECG is normal and the patient is passing urine. If the initial potassium is < 3.5 mmol/l, start replacement before insulin infusion to avoid severe hypokalaemia and its complications of arrhythmias or respiratory muscle weakness.[11] Four-hourly potassium monitoring will guide the need for replacement, as shown in Table III.

Table III. Guide to potassium replacement

Serum K^+	Treatment
<3.0 mmol/l	- 40 mmol KCl per litre IV fluid
3.1 - 4.0 mmol/l	- 30 mmol KCl per litre IV fluid
4.1 - 5.5 mmol/l	- 20 mmol KCl per litre IV fluid
>5.5 mmol/l	- omit KCl

13.5.3.4 Bicarbonate

The use of bicarbonate in the treatment of DKA is controversial. In both prospective and retrospective studies of patients in DKA, treated with or without sodium bicarbonate, there were no differences in cardiac or neurological function, incidence of hypokalemia or hypoglycaemia, or rate of recovery from ketoacidosis.[14-16] There are no prospective randomised studies that have used bicarbonate in patients with a pH < 6.9. To date, evidence does not justify the use of bicarbonate in the treatment of DKA in general.[17]

Author: Daksha Jivan
Editors: Ankia Coetzee, Zaheer Bayat and Aslam Amod

References

1. Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev. 1999 Nov; 15(6):412-26.
2. Coetzee A, Hoffman M, Ascott-Evans BAE. South African Medical Journal 2015; 105(9):756-9. DOI:10.7196/SAMJnew.7889.
3. Sheikh-Ali M, Karon BS, Basu A, et al. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? Diabetes Care 2008; 31(4):643-7.
4. Kitabchi A E, et al. Management of hyperglycemic crises in patients with diabetes. Diabetes Care 2001(24); 131-53.
5. Fisher J N, Shahshahani M N, Kitabchi A E. Diabetic ketoacidosis: low dose insulin therapy by various routes. N Engl J Med. 1977;297(5):238-41.
6. Alberti K G, Hockaday T D, Turner R C. Small doses of intramuscular insulin in the treatment of diabetic "coma". Lancet. 1973;2(7828):512-22.
7. Clumeck N, Detroyer A, Naeije R, et al. Small intravenous insulin boluses in the treatment of diabetic coma. Lancet. 1975;2(7931):416.
8. Hayton W, Grisafe J A. Pharmacokinetics – dosing regimens for insulin. Diabetes. 1976;25:771-5.
9. Umpierrez G E, Cuervo R, Karabell A, et al. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care. 2004; 27:1873-8.
10. Umpierrez G E, Latif K, Stoever J, et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med. 2004;117:291-6.
11. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycaemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-1343.
12. Eledrisi MS, Alshanti MS, Shah MF, et al. Overview of the diagnosis and management of diabetic ketoacidosis. Am J Med Sci. 2006;331(5):243-251.
13. Jivan D. 2011. A comparison of the use of normal saline versus Ringer's lactate in the fluid resuscitation of diabetic ketoacidosis, MMed thesis, University of the Witwatersrand. http://wiredspace.wits.ac.za//handle//10539/12476. Published March 4, 2013. Accessed April 15, 2017.
14. Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med. 1986;105:836-840.
15. Viallon A, Zeni F, Lafond P, et al. Does bicarbonate therapy improve the management of severe diabetic ketoacidosis? Crit Care Med. 1999;27:2690-2693.
16. Lever E, Jaspan JB. Sodium bicarbonate therapy in severe diabetic ketoacidosis. Am J Med. 1983;75:263-268.
17. Chua HR, Schneider A, Bellomo R. Bicarbonate in diabetic ketoacidosis – a systematic review. Ann Intensive Care. 2011;1(1):23.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 14: In-hospital management of hyperglycaemia

SEMDSA 2017 Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Inpatient hyperglycaemia is defined as a blood glucose level > 7.8 mmol/l	B
Efforts should be made to monitor and avoid hypoglycaemia as it has unequivocally been associated with an increased mortality	A
HbA_{1c} should be performed in all patients with IHH at the time of first detection, unless performed in the prior 2-3 months	C
Bedside blood-glucose (BG) monitoring is a useful tool to monitor response to therapy and helps to guide titration of antihyperglycaemic therapy, especially insulin	C
Fasting and preprandial blood glucose targets generally should be < 8 mmol/l, and random glucose values < 10 mmol/l.	C
Insulin therapy is the preferred form of treatment of in-hospital hyperglycaemia (IHH)	B
The use of "sliding-scale insulin" regimen is not recommended	A
In patients who are maintained nil per os, prandial insulin dose should be suspended. Patients previously on basal insulin , should be maintained on this therapy	B
More frequent blood glucose monitoring should be done in patients who are receiving glucocorticoid therapy	C
Among non-critically ill patients, scheduled subcutaneous insulin consisting of three separate components, basal, nutritional, and correctional doses, is the preferred method for achieving and maintaining glucose control	A
Critically-ill patients in ICU and high-care settings are best managed with intravenous insulin therapy using a validated insulin infusion protocol	C
With regards to enteral feeds, in patients with diabetes the use of diabetes-specific formulas is recommended	B
In patients receiving total parenteral nutrition(TPN) , insulin can be added to the TPN solution to maintain euglycaemia	B
Following discharge, patients should be screened for diabetes after 6 weeks	C

14.1 Introduction

Hyperglycaemia is commonly encountered among hospitalised patients with some studies reporting a prevalence of 39.3%.[1] It is the fourth most common condition listed on all hospital discharge forms and can occur in patients with or without diabetes mellitus(DM).[2,3] Traditionally in-hospital hyperglycaemia (IHH) has been referred to as "stress hyperglycaemia" and despite being common, many patients remain undiagnosed. Even when recognised, it is often overlooked and treatment is suboptimal.[4] Putative mechanisms for "stress hyperglycaemia" include increased circulating levels of pro-inflammatory cytokines and counter-regulatory hormones caused by acute illness.

Initially this was thought to be an adaptive mechanism with possible benefits, however this myth has been dispelled by overwhelming evidence indicating that IHH is associated with adverse clinical outcomes and increased mortality.[2,5,6] IHH correlates with the length of hospitalisation, number of rehospitalisations, morbidity and mortality.[4] Hyperglycaemia per se may be associated with an enhanced risk for infection as a result of impairment of the innate immune system. It has also been demonstrated to potentiate coagulation and increase the risk of thrombosis. These effects are further exacerbated in the presence of systemic inflammation.[7-9] The management of hyperglycaemia in hospital can be challenging due to variations in nutrient composition, changes in the frequency and timing of food intake, usage of diabetogenic drugs and the development of renal or other organ dysfunction.

14.2 Definition and aetiology of hyperglycaemia in hospital

The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) consensus statement on inpatient glycaemic control defines hyperglycaemia as a blood

glucose level > 7.8 mmol/l.[2] Three categories of hyperglycaemia can be identified:

1. Known diabetes: past history of DM has been documented
2. Unrecognised DM: patients with DM but previously undiagnosed. This requires confirmation by standard diagnostic criteria after hospitalisation
3. Hospital-related hyperglycaemia: hyperglycaemia occurring during hospitalisation but reverts to normal after discharge.

Distinguishing between categories of hyperglycaemia at the bedside may be difficult, but in general does not impact fundamentally on management principles. Following discharge, it is important to investigate patients appropriately for DM.

14.3 HbA_{1c} measurement

In patients without a history of diabetes, an elevated HbA_{1c} is suggestive of unrecognised DM whilst a normal HbA_{1c} favours stress hyperglycaemia. It is also likely that patients with an elevated HbA_{1c} would require ongoing anti-hyperglycaemic therapy upon discharge from hospital. A normal HbA_{1c} would suggest that the hyperglycaemia may resolve following resolution of the acute illness. HbA_{1c} determination is recommended in all patients with IHH at the time of first detection, unless performed in the prior 2-3 months. Important caveats however do exist, and need to be taken into consideration when interpreting HbA_{1c} within the context of the underlying illness, use of blood products etc.

14.4 Blood glucose monitoring

There are no data to support specific recommendations regarding glucose monitoring. Bedside blood-glucose (BG) monitoring is a useful tool to monitor response to therapy and helps to guide titration of antihyperglycaemic therapy, especially insulin. In addition, BG monitoring is vital in detecting hypoglycaemia, which is an obstruction to the achievement of good glycaemic control and an important cause of morbidity. BG monitoring with use of point-of-care (POC) glucose meters is performed before meals and at bedtime in most inpatients who are eating usual meals.[2] However, the frequency and timing of bedside BG monitoring must be individualised. If intensification of insulin therapy is desired, 2-hour post-prandial BG levels should ideally also be performed. Postprandial testing assists in optimal insulin dose titration. BG monitoring should also be performed at 2am (overnight) if nocturnal hypoglycaemia is a concern. Patients who are receiving continuous enteral or parenteral nutrition require BG monitoring every 4 to 6 hours. Healthcare institutions should have standardised treatment protocols that aim to prevent and address mild, moderate and severe hypoglycaemia appropriately. Healthcare workers should be educated about risk factors for hypoglycaemia, such as a sudden reduction/cessation of oral intake or discontinuation of enteral or parenteral nutrition.

Continuous glucose monitoring (CGM) systems have the potential to detect hypoglycaemia more effectively than POC meters. However, there is currently no evidence that employing CGM translates into better glycaemic control. Therefore, CGM is not recommended in adult hospitalised patients until studies are able to show greater efficacy and safety compared to POC meters.

14.5 Glycaemic Targets in non-critically ill patients

Recommendations are based on clinical experience and judgement since there are no prospective, randomised, controlled trials providing clear evidence for specific blood glucose goals. Fasting and preprandial blood glucose targets generally should be < 8 mmol/l, and random glucose values < 10 mmol/l. More stringent targets may be appropriate for stable patients with previous tight glycaemic control, provided these targets can be safely achieved

14.6 Pharmacological therapy for hyperglycaemia in hospitalised patients

14.6.1 Oral and non-insulin injectable agents

In general, oral agents are considered unsuitable for in-hospital management of hyperglycaemia. Sulphonylureas have been associated with severe and prolonged hypoglycaemia in patients with reduced or limited oral intake.[11] Thiazolidinediones have a delayed onset of action and are also contraindicated in patients with congestive heart failure or in those with haemodynamic instability.[12] Metformin has been associated with lactic acidosis, and risk factors for this complication include cardiac disease, decompensated chronic heart failure, hypoperfusion, renal insuffciency, advanced age, and chronic pulmonary disease.[13] Many of these conditions cluster amongst hospitalised patients, and are either relative or absolute contraindications to metformin use, making metformin an unfavourable choice for therapy. Metformin should be suspended in patients requiring intravenous radio-contrast 48 hours before the planned administration and restarted no sooner than 48 hours after the procedure.

No large-scale studies have investigated the efficacy, safety and outcomes of oral agents in hospitalised patients. Furthermore, oral agents cannot be titrated rapidly to achieve desired glycaemic targets, and therefore have a limited role to play in the treatment of IHH. They should be reserved for mild hyperglycaemia in non-critically ill patients with previously well-controlled diabetes who eat regular meals and in whom there are no specific contraindications to therapy.[1,5] Information on the use of incretin therapy including injectable non-insulin therapies such as glucagon-like peptide-1 (GLP-1) analogues and oral dipeptidyl-peptidase 4 (DPP-4) inhibitors are limited to small studies in specific groups of patients and are generally well tolerated. Treatment with sitagliptin plus basal insulin was shown to be as effective and safe as basal-bolus insulin regimen in patients with type 2 diabetes in the non-intensive-care setting.[10] However, insulin therapy remains the preferred method for achieving acceptable glucose control in the hospital setting.[2]

14.6.2 Insulin

Insulin therapy forms the basis of treatment for IHH. It can facilitate more effective glycaemic control compared to oral and non-insulin injectable agents. Insulin is the most potent agent available against hyperglycaemia, has a more rapid onset of action compared to oral agents, and can easily be titrated and adapted to optimise the glycaemic control of in-hospital patients

with varying therapeutic requirements. Although insulin is the ideal agent for IHH, the type of insulin regimen employed is crucial to the successful management of hyperglycaemia.

Insulin may be administered subcutaneously (SC) or intravenously (IV). SC insulin therapy can be administered as basal-bolus therapy, sliding-scale insulin therapy, a split-mixed regimen of neutral protamine Hagedorn (NPH) insulin and regular insulin, or basal insulin with correction doses of short-acting insulin. Basal-bolus therapy, the most intensive regimen, is ideal for the management of IHH, since it addresses both basal requirements and prandial glucose excursions. **Sliding-scale insulin therapy is inferior to basal-bolus therapy with respect to glycaemic control and is not recommended**. Split-mixed NPH and regular insulin administered twice daily before breakfast and supper have been shown to be comparable to basal-bolus therapy, but lack the flexibility of basal-bolus, in that they require strict adherence to scheduled meals. IV insulin is generally reserved for the critical care environment. Caution should be exercised before implementing IV therapy outside the critical care setting, since inadequate monitoring and poorly trained staff can lead to morbidity and mortality from hypoglycaemia.

With respect to the selection of insulin type, most studies of IHH have employed the use of analogue insulins. Short-acting human insulins are likely to have similar efficacy but slower onset of action compared to rapid-acting insulin analogues. Rapid-acting insulin analogues, such as insulin aspart, lispro and glulisine, which can be injected just a few minutes before the meal, would be beneficial in the hospital setting where the timing of meals may vary.

14.7 Management in non-critically ill patients

Oral agents are generally considered unsuitable and insulin remains the ackbone of anti-hyperglycaemic therapy in-hospital. However, situations where oral agents would be acceptable do exist and include patients with mild hyperglycaemia and previously well-controlled diabetes who are eating regular meals and in whom there are no specific contraindications.[1,5] Stable patients with type 2 diabetes who use insulin at home should continue their pre-admission insulin regimen, with adjustment as required. Those on oral agents alone can safely be switched to insulin in-hospital.

Sliding-scale insulin (SSI) therapy, though widely utilised, is not recommended. It has been shown to be inferior to basal-bolus insulin therapy for glucose control in non-critically ill patients with type 2 diabetes.[14] SSI therapy is reactive in its approach, due to the fact that hyperglycaemia is only treated after it has occurred. It has been associated with higher rates of both hyper- and hypoglycaemia.[15] The Randomized Study of Basal Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes (RABBIT 2 trial) clearly demonstrated that a proactive approach utilising the basal-bolus insulin algorithm is simple and more effective than SSI therapy with respect to glucose control in non-critically ill patients with type 2 diabetes.[14]

The preferred method for achieving and maintaining glucose control is **scheduled SC insulin** therapy consisting of three separate components ie. basal, nutritional (prandial), and correctional (supplemental) doses.[16] Prandial insulin provides enough insulin to cover caloric exposure at mealtimes, during IV fluid therapy, total parenteral nutrition and enteral tube feeding. However, prandial insulin does not cater for pre-meal hyperglycaemia. Therefore, correction dose or "supplemental" insulin is needed in addition to scheduled prandial and basal insulin to correct pre-meal hyperglycaemia.[16]

14.7.1 How to initiate scheduled SC insulin therapy

When starting insulin therapy for the first time in hospital, it is appropriate to estimate the daily insulin requirement for each individual. Fifty per cent of the total daily dose (TDD) of insulin should be prescribed as basal insulin and the remaining 50% should be divided equally between meals as either short- or rapid-acting insulin. The estimated TDD requirement can be based on a patient's body weight and depends on the degree of insulin resistance. The initial dose should be between 0.2-0.5 units/kg body weight. It is important to note that the initial dose of insulin is only an estimate and does not usually provide ideal control. The response to insulin must be assessed frequently and on an ongoing basis, with appropriate titration of the insulin dose to achieve control. Various factors may affect the optimal glycemic control in the in-patient setting. This includes but is not limited to: predetermined meal-times, sedentary behaviour as well as medications and therapies that may alter insulin sensitivity. Depending on the glycaemic target and response to insulin, the dose is adjusted accordingly. These dose alterations depend on the results of bedside glucose monitoring, whilst attempts are made to minimise the risk for hypoglycaemia.

14.7.2 Supplemental (Correction dose) Insulin

Patients receiving scheduled SC insulin may continue to have hyperglycaemia for a variety of reasons, and may principally be due to suboptimal insulinisation. In this instance, small supplementary doses of regular insulin or a rapid-acting analogue can be given, in addition to any scheduled insulin doses. It cannot be overemphasised that supplemental insulin, also referred to as "correction dose" of insulin, is not intended to replace scheduled insulin[17], but rather to augment it. For example, if patients have been prescribed prandial insulin but continue to have hyperglycaemia, they should receive the scheduled prandial dose PLUS the correction dose. Patients being kept NPO that develop hyperglycaemia may also benefit from correction dose insulin at 6 hourly intervals.

Correction doses can either be based on a predetermined scale (Table I) or by calculation using accepted formulae. Using a predetermined scale to advise on correction (supplemental) dosing is simpler and takes the level of hyperglycaemia and clinical assessment of insulin sensitivity into consideration. An example of a correction dose scale is shown in Table I. Another method to calculate the correction dose uses the correction factor (CF), also known as the insulin sensitivity factor. This provides an index of expected reduction in glucose with each unit of insulin administered. The CF is calculated using the so-called "rule of 100" or "rule of 85". This is done by dividing either 100 (for rapid-acting insulin) or 85 (for short-acting insulin) by

Table I: Insulin Correction Dose scale

Bedside BG (mmol/l)*	LEVEL 1	LEVEL 2	LEVEL 3
8.0-10.0	1	2	3
10.1-12.0	2	4	6
12.1-14.0	3	6	9
14.1-16.0	4	8	12
16.1-20.0	5	10	15
> 20	6	12	18

Use of this scale depends on fasting or pre-meal BG readings*
Select the level of the scale based on the patient profile :
LEVEL 1: Insulin sensitive patients (eg. patients who are not eating, elderly patients, and those with impaired renal function)
LEVEL 2: Usual patients (eg. patient who is able to eat all or most of his/her meals)
LEVEL 3: Insulin resistant patient (eg. patients receiving glucocorticoids and those treated with more than 80 U/d before admission)
The "Correction Dose" is to be added to scheduled insulin dose.
Correction doses administered at bedtime should be reduced by 50%.
If a patient develops hypoglycaemia or has a history of hypoglycaemia, decrease regular or rapid-acting insulin from the insulin-resistant to the usual column or from the usual to the insulin-sensitive column

Table I has been adapted from Umpierrez et al[18] and Magaji et al[19]

the patient's total daily insulin dose (TDD). Correction Dose = (Actual blood glucose - target blood glucose) divided by CF.

Correction doses should generally not be given within four hours of each other, and should be avoided if frequent, severe or recent episodes of hypoglycaemia have occurred. The amount of insulin used as correction dose therapy may be used to guide further changes in scheduled insulin doses. Approximately 80% of the total daily correction dose can be added to the scheduled insulin for the following day, 50% of which can be added to the basal insulin component, and the remaining 50% added to prandial component with doses equally divided among the meals.

14.7.3 Patient receiving enteral feeds

Enteral feeding may cause or exacerbate IHH, resulting in adverse outcomes. In patients with diabetes the use of diabetes-specific formulas is associated with improved glycaemic control when compared to standard formulas.[20] Enteral feeds, may be administered on a continuous basis, as boluses or in some instances nocturnally scheduled. Various strategies of insulin administration including: daily long acting insulin analogues; pre-mixed insulins and 12 hourly NPH with or without scheduled regular insulin 6 hourly.

Bolus enteral feeds mimic the usual prandial glucose excursions, and are probably best treated with basal-bolus therapy. The timing of bolus doses must coincide with delivery of the bolus enteral feeds. In addition, basal insulin would still be required to address fasting and inter-feed glycaemia. Patients receiving only nocturnal enteral feeds can be managed with NPH insulin, administered upon commencement of the feed. Any other prandial caloric exposure can be covered with scheduled bolus doses of regular insulin. The major concern with insulin therapy in patients receiving enteral feeds is the risk of hypoglycaemia if feeding is suspended. Therefore, protocols need to be in place that will enable staff to pre-empt and react to such occurrences promptly. If enteral feeding is stopped, insulin should also be immediately withheld and a 10% dextrose-containing infusion commenced to prevent hypoglycaemia.

14.7.4 Patients receiving total parenteral nutrition (TPN)

Total parenteral nutrition (TPN) associated hyperglycaemia has also been linked with adverse clinical outcomes.[21] Regular insulin can be added to the TPN solution to maintain euglycaemia. The starting dose can be commenced at 0.1 units/g of carbohydrate contained in the TPN (one unit of regular insulin per 10 g of carbohydrate). In cases of severe hyperglycaemia, it is advisable to use IV insulin therapy. In addition, IV insulin therapy may be a useful way of determining the total daily insulin requirements. Once glucose control has stabilised, IV insulin therapy can be replaced with the addition of regular insulin to the TPN, at a dose of approximately 80% of the TDD. In patients with type 2 diabetes, it may be possible to provide half the TDD as basal insulin, and the remaining dose as regular insulin into the TPN. SC correction doses of regular insulin are also advised, to deal with hyperglycaemia related to an inadequate TDD prescription. Approximately 80% of the total daily corrective insulin dose can be added to the following day's scheduled insulin.

14.7.5 Patients being maintained nil per os (NPO)

Previously prescribed scheduled prandial insulin doses should be suspended. However, patients who previously received basal insulin (including once-daily, long-acting analogues and once- or twice-daily NPH insulin) should still be maintained on this therapy. Glycaemic targets are maintained with correction doses of regular or short-acting analogue insulin that can be given six hourly (see correction dose calculation). Patients being kept NPO for prolonged periods should be maintained on a dextrose infusion to prevent hypoglycaemia.

14.7.6 Patients using continuous insulin infusion therapy (CSII)

Continuous subcutaneous insulin infusion (CSII) pump therapy, though infrequently utilised in South Africa may be encountered in a few patients. Although continuation of pump therapy is desirable, it is in most instances not possible. The lack of expertise of most health care practitioners (HCP) with this modality renders it undesirable. It is therefore recommended that during hospital admissions, CSII is temporarily stopped unless the attending HCP's have the necessary accredited training and

experience. Whenever CSII therapy is suspended, patients should be converted to subcutaneous insulin therapy until CSII can be recommenced. Where staff and patient have the required competence in insulin pump therapy, CSII may be continued provided this can be accomplished safely and adequate supplies are available. It is necessary to clearly document the details of basal rates, bolus and correction dosing in the treatment chart.

14.7.7 Patients receiving glucocorticoid therapy

Steroid therapy has the potential to induce or exacerbate hyperglycaemia. The use of steroids necessitates greater vigilance with glucose monitoring. Some studies have reported multiple hyperglycemic episodes occurring in 52% of hospitalised patients.[22] The effects of steroids are not necessarily uniform and its glycaemic consequences may possibly be affected by a number of patient factors, route of administration, total administered dose and these require further investigation. However, it has been shown that patients with multiple episodes of hyperglycaemia have more comorbid diseases, longer duration of corticosteroid therapy, and longer duration of hospital stay.[22] The management of glucocorticoid induced hyperglycaemia has not been adequately investigated. The most rational approach is to determine the degree of hyperglycaemia and appropriately intervene with insulin therapy. The type of insulin regimen to be employed is not stipulated but should be able to provide basal, nutritional and supplemental insulin (if required). Current recommendations advise heightened vigilance for hyperglycaemia in the 48 hours after commencing steroids.[2] More frequent BG monitoring assists in determining the development and severity of hyperglycaemia, thereby guiding the need for insulin therapy as well as dosing. However, one important caveat to insulin therapy is to anticipate a reduction in glucose levels when steroid doses are reduced or steroids are withdrawn, which would then require an appropriate reduction in insulin dose or perhaps cessation, depending on BG monitoring.

14.7.8 Perioperative glycaemic management

Hyperglycaemia affects immune function and may increase the risk for infection.[7-9] In patients undergoing surgery, hyperglycaemia per se may adversely affect outcomes by increasing the risk of wound infection. Hyperglycaemia also increases the risk of other postoperative infections.[21] In surgical wards, postoperative wound infections have been shown to be the most common nosocomial infection, an important contributor to morbidity and mortality. Furthermore, wound healing can also be affected.

Strict glycaemic control has been shown to improve surgical outcomes in patients undergoing cardiac surgery and critically ill surgical patients. However, more robust evidence is still needed to confirm the efficacy of tight glycaemic control in preventing perioperative infections.

14.7.9 Discharging patients from hospital

Patients that were previously well controlled on oral agents and are clinically stable, may be recommenced on oral medication prior to discharge, provided they do not have contraindications to oral agents and are maintaining a regular eating pattern. Patients with poor control or contraindications to oral antidiabetic therapy require continuation of insulin therapy. These patients require in-hospital education on insulin self-administration and titration. They also need to be taught to recognise and manage hypoglycaemia. Follow-up must be arranged to reassess control in patients with diabetes.

14.8 Critically ill patients

Acute hyperglycaemia in the intensive care setting is not unusual and results from a number of factors, including stress-induced counter-regulatory hormone secretion, and medications administered in the ICU.[24] Hyperglycaemia in this setting has effects on multiple systems, including the cardiovascular, neurological and immune systems.[24] The results of early studies investigating the advantages of intensive insulin therapy in critical care patients were positive. The landmark study by Van den Berghe *et al*[25] demonstrated impressive benefits of intensive glycaemic control with IV insulin infusion, in predominantly surgical patients admitted to the ICU who required mechanical ventilation. A subsequent analysis of a more heterogeneous ICU population with predominantly medical patients demonstrated a reduction in mortality, length of stay, renal dysfunction and requirement of transfusion among those receiving intensive glycaemic control with an IV insulin infusion protocol.[25]

However, more recent randomised, controlled studies in critically ill patients have not shown the substantial mortality benefits that were previously described. The largest randomised, controlled study, the Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, included 6 104 critically ill patients. Patients were randomised to intensive and conventional treatment groups, with target glucose ranges of 4.5–6.0 mmol/l and ≤ 10.0 mmol/l, respectively. The final mean blood glucose values achieved in the two groups were 6.4 and 8.0 mmol/l respectively. Mortality at 90 days was unexpectedly higher in the intensively treated arm (27.5% vs. 24.9%, $p = 0.02$). The two groups did not differ in terms of days spent in the ICU, hospital stay or days on mechanical ventilation or renal dialysis. Of note, the risk of severe hypoglycaemia was significantly greater in the intensively treated arm (6.8% vs. 0.5%, $P < 0.001$). There were no differences between the two groups for other outcomes. These findings do not diminish the advantages of glycaemic control, but instead indicate that targeting near-normal glucose levels (< 6.0 mmol/l) is not advisable and may, in fact, be detrimental. A meta-analysis of 26 trials that included the NICE-SUGAR study, showed a mortality benefit for intensive glycaemic control among surgical ICU patients only albeit with a significant risk for hypoglycemia.[26]

Based on the available evidence, insulin therapy should be initiated for persistent hyperglycaemia, starting at a threshold of no greater than 10 mmol/l.[2] Once insulin therapy has been commenced, it is recommended that glucose values be maintained between 7.8-10 mmol/l.[2] Although lacking evidence, more stringent goals, such as 6.1–7.8 mmol/l, may be appropriate for selected patients, as long as this can be achieved without significant hypoglycaemia. Targets < 6.1 mmol/, however, are not recommended.

Critically ill patients in ICU and high-care settings are best managed with IV insulin using a well validated insulin infusion protocol. There are a number of published IV insulin infusion protocols that are safe and effective. Before commencement of IV insulin infusion therapy, clinicians should ensure that regular, accurate BG monitoring is feasible. An adequate staff complement and expertise are needed to ensure safe and successful implementation. The insulin infusion protocol must be readily accessible, legible and should specify the adjustments of insulin rates as well as the frequency of BG monitoring, based on the prevailing glucose level. Furthermore, nursing staff in the critical-care setting must be well educated on the selected insulin infusion protocol and importantly, the prevention and management of hypoglycaemia. Once stabilised and the patient is commenced on oral/enteral feeds, transitioning from IV insulin to scheduled SC insulin can be undertaken. SC insulin must overlap with IV insulin infusion for at least one (1) hour before discontinuing IV insulin infusion therapy.

14.9 Hypoglycaemia

Hypoglycaemia has unequivocally been associated with an increased mortality. A protocol should be in place to respond to hypoglycaemia in-hospital. Staff should be aware of the protocol and adequately trained in its implementation. The development of hypoglycaemia should prompt a review of current anti-hyperglycaemic therapy and adjustment if required. All incidents of hypoglycaemia and subsequent changes in treatment must be clearly documented. Staff should be aware of known precipitants of hypoglycaemia such as NPO status, reduction in oral intake, increase in insulin, reduction or interruption in NGT or TPN feeds etc.

Author: Imran Paruk

Editors: Ankia Coetzee and Zaheer Bayat

References :

1. Boord, J. B., Greevy, R. A., Braithwaite, S. S., Arnold, P. C., Selig, P. M., Brake, H., Cuny, J. and Baldwin, D. (2009), Evaluation of hospital glycemic control at US Academic Medical Centers. J. Hosp. Med., 4: 35–44.
2. Moghissi ES, Korytkowski MT, DiNardo MM, et al. American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control. Diabetes Care. 2009; 32: 1119-1131.
3. Wexler DJ, Meigs JB, Cagliero E, et al. Prevalence of hyper- and hypoglycaemia among inpatients with diabetes: a national survey of 44 U.S. hospitals. Diabetes Care. 2007; 30: 367-369.
4. Leite SA, Locatelli SB, Niece SP, Oliveira AR, Tockus D, Tosin T. Impact of hyperglycaemia on morbidity and mortality, length of hospitalization and rates of re-hospitalization in a general hospital setting in Brazil. Diabetol Metab Syndr. 2010 Jul 21;2:49.
5. Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycaemia in hospitals. Diabetes Care. 2004; 27: 553-591.
6. Cheung NW, Li S, Ma G, Crampton R. The relationship between admission blood glucose levels and hospital mortality. Diabetologia. 2008 Jun;51(6):952-5. Epub 2008 Apr 16.
7. Stegenga ME, van der Crabben SN, Blumer RME, et al. Hyperglycaemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. Blood. 2008; 112:82-89.
8. Pickup JC, Chusney GD, Thomas SM, Burt D. Plasma interleukin-6, tumour necrosis factor alpha and blood cytokine production in type 2 diabetes. Life Sci. 2000;67:291–300.
9. Marhoffer W, Stein M, Maeser E, Federlin K. Impairment of polymorphonuclear leukocyte function and metabolic control of diabetes. Diabetes Care. 1992;15:256–260.
10. Pasquel FJ et al. Efficacy of sitagliptin for the hospital management of general medicine and surgery patients with type 2 diabetes (Sita-Hospital): a multicentre, prospective, open-label, non-inferiority randomised trial. The Lancet Diabetes & Endocrinology , Volume 5 , Issue 2 , 125 - 133
11. Bodmer M, Meier C, Krahenbuhl S, et al. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case -control analysis. Diabetes Care. 2008; 31: 2086-2091
12. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med. 2007; 147: 386-399.
13. Dunham DP, Baker D. Use of an electronic medical record to detect patients at high risk of metformin -induced lactic acidosis. Am J Health Syst Pharm. 2006; 63: 657-660.
14. Umpierrez G, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). Diabetes Care. 2007;30:2181-2186.
15. Queale WS, Seidler AJ, Brancati FL. Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. Arch Intern Med. 1997;157:545-552.
16. Magee MF, Clement S. Subcutaneous insulin therapy in the hospital setting: issues, concerns, and implementation. Endocr Pract. 2004;10(suppl 2):81-88.
17. Campbell KB, Braithwaite SS. Hospital Management of Hyperglycaemia. Clinical Diabetes. Volume 22, Number 2, 2004
18. Elia M, Ceriello A, Laube H, et al. Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis. Diabetes Care. 2005;28:2267–2279.
19. Pasquel FJ, Spiegelman R, McCauley M, et al. Hyperglycaemia during total parenteral nutrition: an important marker of poor outcome and mortality in hospitalized patients. Diabetes Care. 2010;33(4):739-741.
20. Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycaemia in hospitalized patients. Endocrine Practice: July 2006, Vol. 12, No. 4, pp. 358-362.
21. Ramos M, Khalpey Z, Lipsitz S, Steinberg J, Panizales MT, Zinner M, Rogers SO. Relationship of perioperative hyperglycaemia and postoperative infections in patients who undergo general and vascular surgery. Ann Surg. 2008;248:585–591.
22. Lewis KS, Lane-Gill SL, Bobek MG, et al. Intensive insulin therapy for critically ill patients. Ann Pharmacother. 2004;38: 1243-1251.
23. Van den Berghe G,Wouters P,Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345: 1359-1367.
24. Griesdale DEG, De Souza RJ, Van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR data. Can Med Assoc J. 2009;180:821-827
25. Guillermo E. Umpierrez, Richard Hellman, Mary T. Korytkowski, Mikhail Kosiborod, Gregory A. Maynard, Victor M. Montori, Jane J. Seley, and Greet Van den Berghe. Management of Hyperglycaemia in Hospitalized Patients in Non-Critical Care Setting: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 97: 16–38, 2012.
26. Magaji V, Johnston JM. Inpatient Management of Hyperglycaemia and Diabetes. Clinical Diabetes 2011 Jan; 29(1): 3-9.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 15: Weight management in type 2 diabetes

SEMDSA Type 2 Diabetes Guideline Expert Committee

SEMDSA 2017 Recommendations	
The body mass index (BMI) and waist circumference of all patients with type 2 diabetes must be recorded at every visit.	C
Modest weight loss (5-10%) in overweight and obese individuals improves glycaemic control and cardiovascular risk factors.	A
For obese or overweight patients with type 2 diabetes who are willing, an intensive lifestyle intervention focusing on diet, physical activity, and behavioural therapy should be available to support >5% weight loss over 6 months. Successful programmes require high frequency contact (weekly for 6 months and at least monthly thereafter for those who achieve their goals). Behavioural therapy can/should be offered in groups.	A
The primary focus of the dietary intervention for weight loss should be on caloric restriction (aim for >500 to 750 kcal deficit/day) irrespective of macronutrient composition, which is less important.	A
Very low calorie diets must not be prescribed in the primary health care setting.	C
For achieving and maintaining weight loss goals, encourage individuals to engage in at least 4 hours of moderate intensity exercise (e.g. brisk walking, dancing, gardening) per week.	
Orlistat is the only weight-loss medication approved in South Africa and can be used as an adjunct to intensive lifestyle interventions in selected patients (BMI ≥ 27 kg/m^2 with diabetes or BMI ≥ 30 kg/m^2 with IGT).	A
When choosing medications for the management of diabetes and co-morbid conditions, always consider the potential effects on weight in obese patients. If weight gain from other glucose therapies is problematic consider switching to drugs with a neutral or beneficial effect on weight (metformin, DPP-4 inhibitors, alpha-glucosidase inhibitors, GLP-1 agonists and SGLT2 inhibitors)	C
Bariatric surgery is a treatment option for obesity and diabetes in patients whose BMI ≥ 35 kg/m^2 and in selected patients with a BMI ≥ 30 kg/m^2 when glucose levels are not controlled despite the best efforts with medications and lifestyle modification.	B

Table I: WHO Classification of Weight by Body Mass Index (BMI) in adults[§]

Classification	International BMI category (kg/m^2)	BMI Category for Asians
Underweight	<18.5	<18.5
Normal weight	18.5–24.9	18.5-22.9
Overweight	25.0–29.9	23.0-24.9
Obese	≥30.0	≥25.0
Class I	30.0–34.9	25.0-29.9
Class II	35.0–39.9	≥30
Class III	≥40.0	

Formula to calculate BMI = weight in kilograms divided by the square of the height in meters (kg/m^2)

[§] WHO/IASO/IOTF, "The Asia-Pacific perspective: Redefining obesity and its treatment. Health communications," 2000. [Online] Available: http://www.wpro.who.int/nutrition/documents/docs/Redefiningobesity.pdf. [Accessed on 20th Februrary' 2017]

The literature review for this guideline involved a Pubmed and Cochrane database review search up to 1 August 2016, as well as a review of Diabetes Guidelines from the ADA, IDF, AHA, and a Joint Statement by International Diabetes Organisations.

Introduction

Obesity is a common association with type 2 diabetes, with a large proportion (80-90%) of patients being overweight or obese. Weight gain is a particularly strong risk factor for the

development of diabetes,[1,2] and a 5 – 10% weight loss has been consistently associated with diabetes prevention (refer to Chapter 27). Current data from the SANHANES-1[3] report show that 1/3 of South African men and 2/3 of women are obese or overweight.[4] The World Health Organisation (WHO) classification for weight is shown in Table I.

Management of obesity is typically multifaceted and involves dietary changes, exercise, behavioural therapy, pharmacotherapy, and surgical options.

Weight-loss goals

The aim in overweight patients with diabetes is to lose a minimum of 5-10% of body weight, as this has been shown to reduce cardiovascular risk factors.[4-6] The optimal amount of weight loss is difficult to ascertain, but a minimum of 15% weight loss has been shown to have a marked impression upon glucose levels[7] and even reversing diabetes.[8] The durability of this approach to diabetes remission though has not been clearly demonstrated, apart from bariatric studies, but does look promising.

Diet

The role of dietary manipulation in diabetes is an evolving one, but when it comes to weight loss, quantity adjustments of the diet in terms of caloric restriction is the most important component, more so than quality adjustments.[9-14] Optional diets include the low fat, low-carbohydrate (may need to adjust hypoglycaemic therapy), and the Mediterranean diet. Very low calorie diets (VLCD) (< 800 calories per day) should only be prescribed in very carefully selected patients[7].

Very low-calorie diets that achieve substantial weight loss have been associated with remission of diabetes , but the practicality and durability of this approach, as mentioned earlier, requires further research[7,8,15]

There is no one diet that is applicable to all patients, and therefore each patient's diet needs to be individualised.

Exercise

Exercise[16,17] is an important component in the management of diabetes, but currently still plays a secondary role to dietary caloric reduction when it comes to weight loss.

With regards to weight loss, physical activity of moderate intensity for longer than 225–420 minutes per week will result in about a 5-7.5 kg weight loss. There is a dose-response relationship between exercise and weight loss, with more exercise leading to greater weight loss. For weight maintenance, after weight loss has been achieved, 200-300 minutes of exercise per week is required.

For people with diabetes at a stable weight, moderate exercise for 150-250 minutes per week is required to prevent weight gain of > 3% in adults. Resistance training has not been shown to be particularly effective for weight loss, although there is limited evidence that it promotes the gain or maintenance of lean mass and loss of body fat during energy restriction. There is also some evidence that resistance training helps improves chronic disease risk factors.[16,17]

Behavioural therapy

Behavioural therapy is an important component in supporting weight loss, and can be offered on an individual and/or group basis to help patients overcome problems and to help them to achieve their goals.[5]

Pharmacotherapy

Currently, only orlistat is approved in South Africa as pharmacotherapy for weight loss, although other medications (phentermine-topamax, lorcaserin, natrexone-bupropion, and liraglutide 3.0mg) are licenced in other countries. Orlistat can be prescribed for patients with diabetes and a body mass index (BMI) ≥ 27 kg/m^2, as well as for those with impaired glucose tolerance and a BMI ≥ 30 kg/m^2. If weight loss is < 5% in 3 months, then the medication must be stopped.[18,19]

The SCALE study examined liraglutide 1.8 mg and 3.0 mg for weight loss in type 2 diabetes;[20] mean placebo corrected weight loss was 2.7% and 4% for the 1.8 mg and 3.0 mg dose, and 20% and 35% of patients lost >5% weight respectively (placebo corrected).

The single exit price including VAT for these drugs as at March 2017 was as follows:

1. Orlistat 120 mg TDS x 28 days: R945.67
2. Liraglutide 1.8 mg/day (registered dose for diabetes) x 30 days: R2145.97.

Drugs with a neutral or beneficial effect on weight, such as metformin, DPP-4 inhibitors, GLP-1 agonists, SGLT2 inhibitors and alpha-glucosidase inhibitors may be the preferred choice of treatment for overweight or obese patients, especially if weight gain is problematic with other therapies.

Bariatric surgery for type 2 diabetes

Bariatric surgery has been a major advancement in the treatment of obese people with diabetes in recent years. It should be considered for patients who have reached physical maturity and have type 2 diabetes with a BMI≥ 35 kg/m^2.[21-31] The surgery must be performed in an experienced multidisciplinary unit. The benefits of surgery extend beyond improving glycaemic control, as multiple other comorbidities are also positively affected. With regards to the complications of diabetes, particularly microvascular and macrovascular complications, cancer and mortality, there is currently only observational data on the influence of bariatric surgery.[31] This data does, however, show some promise with regards to the aforementioned endpoints. Bariatric surgery has been shown to reduce mortality.[42]

Bariatric surgery for patients whose BMI is under 35 kg/m^2 can only be considered in those in whom glucose levels are not controlled by adequate medication usage and appropriate lifestyle changes.[31-41]

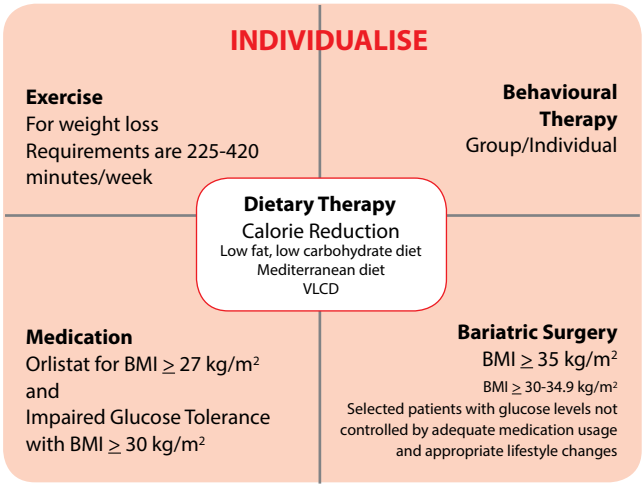
The BMI threshold in patients of Asian descent should be 2.5 kg/m^2 lower than for Caucasians (ADA recommendation).

Bariatric surgery is not without its complications, and therefore regular structured follow-up is essential to pre-empt potential complications, with particular attention being paid to those complications relating to nutritional deficiencies.[43]

The choice of procedure (Roux-en Y gastric bypass, biliopancreatic diversion with duodenal switch, sleeve gastrectomy and gastric banding) is to be individualised by the Bariatric Centre.

Summary

Weight loss for overweight/obesity in patients with diabetes must be considered as an integral part of management. The optimal means to lose weight involves multiple options, and must be individualised for each patient. Bariatric surgery is the most effective intervention for those who fail to achieve weight loss goals with lifestyle modification but is not without cost or complications.



Author: Wayne May
Editors: Aslam Amod and Fraser J. Pirie

Bibliography

1. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med. 1995; 122(7):481-486.
2. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care. 1994; 17(9):961-969.
3. Shisana O, Labadarios D, Rehle T, Simbayi L, Zuma K, Dhansay A, Reddy P, Parker W, Hoosain E, Naidoo P, Hongoro C, Mchiza Z, Steyn NP, Dwane N, Makoae M, Maluleke T, Ramlagan S, Zungu N, Evans MG, Jacobs L, Faber M, & the SANHANES-1 Team (2014) South African National Health and Nutrition Examination Survey (SANHANES-1): 2014 Edition. Cape Town: HSRC Press
4. Wing RR , Lang W, Wadden TA., Safford M, Knowler WC, Bertoni AG et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011; 34(7):1481-1486
5. Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study Look AHEAD Research Group. Obesity (Silver Spring) 2014; 22:5–13
6. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369:145–154
7. Lean M. VLED and formula LED in the management of type 2 diabetes: defining the clinical need and research requirements. Clinical Obesity. (2011) 1, 41–49
8. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalization of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia 2011; 54:2506–2514
9. Foster GD, Wyatt HRHill JO, Makris AP, Rosenbaum DLet al Weight and Metabolic Outcomes after 2 Years on a Low-Carbohydrate Versus Low-Fat Diet. Ann Intern Med. 2010 August 3; 153(3): 147–157
10. Sacks FM, Bray GA, Carey VJ., Smith SR, Ryan DH , Anton SD, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009; 360:859–873
11. Shai I, Shwarzfuchs D, Henkin Y, et al. Weight loss with low carb, low fat or mediterranean diet. New Engl J Med. 2008; 359:229-241.
12. Esposito K, Maiorino MI, Ciotola M, Di Palo C, Scognamiglio P, Gicchino M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. Ann Intern Med. 2009; 151:229-241.
13. Davis NJ, Tomuta N, Schechter C, Isasi CR, Segal-Isaacson CJ, et al. Comparative Study of the Effects of a 1-Year Dietary Intervention of a Low-Carbohydrate Diet Versus a Low-Fat Diet on Weight and Glycemic Control in Type 2 Diabetes. Diabetes Care July 2009 vol. 32 no. 7 1147-1152
14. Iqbal N, Vetter ML, Moore RH, Chittams JL, Dalton-Bakes CV, Dowd M, et al. Effects of a low-intensity intervention that prescribed a low-carbohydrate vs. a low-fat diet in obese, diabetic participants- 2 year Obesity 2010 Sep;18(9):1733-8
15. Jackness C, Karmally W, Febres G, et al. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and b-cell function in type 2 diabetic patients. Diabetes 2013; 62:3027–3032
16. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW et al. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Medicine and Science in Sports and Exercise. 2009; 41(2):459-471.
17. Colberg SR, Albright AL, Blissmer BJ, Braun B, Chasan-Taber L, Fernhall B et al.Exercise and type 2 diabetes: joint position statement. Medicine and Science in Sports and Exercise. 2010;42(12):2282-2303
18. Torgenson JS, Boldrin MN, Hauptman J, et al. XENical in the prevention of diabetes in obese subjects (XENDOS) study. Diabetes Care. 2004;27: 155-161.
19. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med. 2005; 142:532-546.
20. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes. JAMA. 2015;314(7):687. doi:10.1001/jama.2015.9676.
21. Dixon JB, O'Brien PE, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes. JAMA. 2008; 299(3):316-323.
22. Sjöström L, Lindroos LAK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004;351(26):2683W.
23. Schauer PR, Bhatt DL, , Kirwan JP, Wolski K, Brethauer SA, Navaneethan S. et al for the STAMPEDE Investigators. Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 3-Year Outcomes. N Engl J Med 2014; 370:2002-2013
24. Mingrone G, Panunz S, De Gaetano A, Guidone C, Iaconelli A, Leccesi Let al . Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes. N Engl J Med 2012; 366:1577-1585
25. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2015; 386: 964–973
26. Cummings DE, Arterburn DE, Westbrook EO, et al. Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomised controlled trial. Diabetologia 2016; 59: 945–953
27. Halperin F, Ding SA, Simonson DC, et al. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. JAMA Surg 2014; 149: 716–726
28. American Diabetes Association. 6. Obesity management for the treatment of type 2 diabetes. Diabetes Care 39 (Suppl. 1), S47–S51 (2016).
29. International Diabetes Federation. The International Diabetes Federation has released its Position Statement on Bariatric Surgery [homepage on the Internet]. c2011 [cited 2012 Mar 8]. Available from: http://www.idf.org/webdata/docs/IDF-Position-Statement-Bariatric-Surgery.pdf.
30. Bariatric surgery and cardiovascular risk factors. A scientific statement from the American Heart Association. Circulation. 2011; 123: 1683-1701.

31. Rubino F, Nathan DM, Eckel RH, et al. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care. 2016; 39: 861-877
32. Panunzi S, De Gaetano A, Carnicelli A, Mingrone G. Predictors of remission of diabetes mellitus in severely obese individuals undergoing bariatric surgery: do BMI or procedure choice matter? A meta-analysis. Ann Surg 2015; 261: 459–467
33. Panunzi S, Carlsson L, De Gaetano A, Peltonen M, Rice T, Sjöström L Et al Determinants of Diabetes Remission and Glycemic Control After Bariatric Surgery. Diabetes Care 2016 Jan; 39(1):166-74
34. Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. JAMA 2013; 309: 2240–2249
35. Courcoulas AP, Goodpaster BH, Eagleton JK, et al. Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. JAMA Surg 2014; 149: 707–715
36. Liang Z, Wu Q, Chen B, Yu P, Zhao H, Ouyang X. Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: a randomized controlled trial. Diabetes Res Clin Pract 2013; 101: 50–56
37. Wentworth JM, Playfair J, Laurie C, et al. Multidisciplinary diabetes care with and without bariatric surgery in overweight people: a randomised controlled trial. Lancet Diabetes Endocrinol 2014; 2: 545–552
38. Parikh M, Chung M, Sheth S, et al. Randomized pilot trial of bariatric surgery versus intensive medical weight management on diabetes remission in type 2 diabetic patients who do NOT meet NIH criteria for surgery and the role of soluble RAGE as a novel biomarker of success. Ann Surg 2014; 260: 617–622
39. Cohen RV, Pinheiro JC, Schiavon CA, Salles JE, Wajchenberg BL Effects of Gastric Bypass Surgery in Patients With Type 2 Diabetes and Only Mild Obesity. Diabetes Care 2012; 35: 1420–1428
40. ASMBS Clinical Issues Committee. Bariatric surgery in class I obesity (body mass index 30–35kg/m2). Surgery for Obesity and Related Diseases 9 (2013) e1–e10
41. Harold E. Lebovitz. Metabolic Surgery for Type 2 Diabetes with BMI <35 kg/m2. Obes Surg (2013) 23: 800–808
42. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, et al. Effects of Bariatric Surgery on Mortality in Swedish Obese Subjects N Engl J Med 2007;357:741-52
43. Wolfe BM, Belle SH. Long-term risks and benefits of bariatric surgery: a research challenge. JAMA 2014; 312:1792–1793

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 16: Cardiovascular risk and the management of dyslipidaemia in patients with type 2 diabetes mellitus

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Type 2 diabetes is considered a coronary artery disease risk equivalent and dyslipidaemia as well as other cardiovascular risk factors should be looked for and aggressively treated in every patient with diabetes	A
In most diabetic subjects, the risk is due to LDL that contributes the bulk of total cholesterol but hypertriglyceridaemia may also contribute to atherosclerotic cardiovascular risk and may in some cases cause pancreatitis. Hypertriglyceridaemia of 10 to 15mmol/L requires urgent intervention to diet and diabetes control to avoid pancreatitis.	B
Lowering LDL-cholesterol, particularly with statin therapy, reduces the risk of major cardiovascular events.	A
Statins are the first-line agents for lowering LDL-cholesterol levels.	A
Achieving the LDL-cholesterol level is the primary goal of therapy	A
Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for all patients with type 2 diabetes who: ◦ Have existing cardiovascular disease (i.e. ischaemic heart disease, cerebrovascular disease or peripheral vascular disease). ◦ Have chronic kidney disease (eGFR < 60 ml/minute/1.73m^2). ◦ Are either older than 40 years of age or have diabetes of longer than 10 years' duration, with one or more additional cardiovascular risk factor, i.e. hypertension, cigarette smoker, low HDL-cholesterol level, family history of early coronary heart disease, and any albuminuria	A
Monitor LDL-cholesterol 3 months after therapy is instituted or therapy adjusted and then annually once at target.	C

16.1 Introduction

Although hyperglycaemia is the most obvious feature of type 2 diabetes mellitus it is conceptually useful to think of type 2 diabetes as a vasculopathic disorder that damages both small (microvascular) and large (macrovascular) vessels. Dyslipidaemia is a major contributor to macrovascular disease, or atherosclerosis, which accounts for up to 70% of all diabetic mortality. Type 2 diabetes is therefore considered a coronary artery disease risk equivalent and dyslipidaemia as well as other cardiovascular risk factors should be looked for and aggressively treated in every patient with diabetes.[1]

16.2 Managing cardiovascular risk in type 2 diabetes

The risk of CVD for people with type 2 diabetes is increased two to three fold in men and three to five fold in women compared with people without diabetes.[2] Abnormal glucose metabolism (dysglycaemia) that does not meet diagnostic criteria for diabetes is already associated with increased cardiovascular risk. Outcomes following myocardial infarction, stroke or revascularization are also worse in patients with diabetes compared to non-diabetic individuals. Atherosclerosis is often accelerated, severe and diffuse in diabetes. Chronic hyperglycaemia is an additional risk factor for atherosclerosis in patients with diabetes and adds to the well-known standard risk factor burden of race, gender, hypertension, dyslipidaemia, smoking, social deprivation and obesity.[3] Table I summarises the traditional modifiable risk factors for CVD and the recommended target values in diabetes.

Estimating CVD risk in type 2 diabetes

Risk scoring in diabetes is useful in obtaining more accurate numeric risk estimates, but is generally not needed for deciding whether to start lipid-lowering therapy or not as diabetes is considered to be a coronary risk equivalent and therapy is therefore indicated in almost all cases.[4,5] The ACC/AHA guidelines also recommend more aggressive lipid-lowering therapy if the individuals calculated risk is high.[6]

16.3 The metabolic syndrome

The metabolic syndrome, or insulin resistance syndrome, has become one of the major public health challenges worldwide[7]. Over the past few decades the prevalence has increased exponentially, affecting up to 25% of Western populations. This increase has paralleled the global epidemic of obesity.

The metabolic syndrome increases the risk of developing diabetes approximately fivefold, and doubles the risk of atherosclerotic

Table I: CVD risk factors and targets for patients with type 2 diabetes

Traditional CVD risk factors	Targets
Cigarette smoking	Cessation
Dyslipidaemia	
Total cholesterol	<4.5 mmol/L
LDL cholesterol	<1.8 mmol/L
HDL cholesterol	> 1.0 mmol/L (men) >1.2 mmol/L (women)
Triglycerides	<1.7 mmol/L
Obesity	
Waist circumference	<94 cm (men); <90 cm (men of South Asian descent) <80 cm (women)
Body mass index	<25 kg/m^2
Hypertension	
Systolic blood pressure	<140 mmHg
Diastolic blood pressure	<90 mmHg

LDL = low density lipoprotein; HDL = high density lipoprotein

cardiovascular disease.[6] Features characteristic of the syndrome include abdominal obesity, atherogenic dyslipidaemia (elevated serum triglyceride and lowered HDL cholesterol), hypertension and elevated fasting glucose. Other ancillary conditions may include the polycystic ovarian syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD) and sleep apnoea.

Criteria for the diagnosis of the metabolic syndrome are shown in Table II. The presence of three of the five listed criteria is sufficient to make a diagnosis of the metabolic syndrome. Drug treatment specifically targeted at any one of criteria 2-5 makes that criterion positive even if the measured variable falls below the cutoff. Population- and country-specific definitions of elevated waist circumference are provided in Table III.

Pharmacotherapy may play a role in the management of the metabolic syndrome, but lifestyle change, namely diet adjustment, weight loss and regular exercise, are the cornerstone of therapy. Lifestyle change can delay, or even prevent, the onset of type 2 diabetes in patients with the metabolic syndrome (Refer to "Prevention and delay of type 2 diabetes mellitus"). Statins are also frequently used in subjects with the metabolic syndrome. With statin therapy, the risk of developing diabetes is increased by a rate of 0.1% per year. However most people aged 50 years or older have a 10-year risk of a cardiovascular event exceeding 10%. Combining information from 13 individual studies (involving a total of 91 140 patients) showed that treating 255 patients with statins for 4 years led to one extra case of diabetes mellitus, whereas 5.4 cardiovascular events were prevented. Therefore the cardiovascular benefit of statin therapy far exceeds the risk of developing diabetes.[8]

Table II. Harmonised criteria for the clinical diagnosis of the metabolic syndrome[7]

Measure	Categorical cut points
Elevated waist circumference	Population- and country- specific definitions (Table III)
Elevated triglycerides§	≥ 1.7 mmol/l
Reduced HDL cholesterol§	Men < 1.0 mmol/l Women < 1.3 mmol/l
Elevated blood pressure§	Systolic ≥ 130 mmHg and/or Diastolic ≥ 85 mmHg
Elevated fasting glucose§	≥ 5.6 mmol/l

§If the patient is receiving treatment directed at this variable the criterion is counted as positive

Table III. Population- and relevant country-specific definitions of elevated waist circumference

	Men	Women
Sub-Saharan Africa	≥ 94 cm	≥ 80 cm
Europid	≥ 94 cm	≥ 80 cm
Asian	≥ 90 cm	≥ 80 cm
Chinese	≥ 85 cm	≥ 80 cm

16.4 Diabetic dyslipidaemia

Atherosclerosis accounts for up to 70% of all diabetic mortality in white, mixed race and Asian patients. Atherosclerosis is still uncommon in black patients, but is on the increase. Lipid disturbances are common in diabetes and are an important contributor to the high incidence of vascular disease. Lipid abnormalities should therefore be looked for and treated in every patient with diabetes.

The most frequently encountered lipid disturbances in type 2 diabetes are mildly to moderately increased serum triglycerides and decreased HDL cholesterol. Moderate triglyceride elevation (2-5 mmol/L) usually indicates that the concentration of remnant lipoproteins (partially metabolised VLDL and chylomicrons) is increased. Remnant lipoproteins are highly atherogenic. LDL-cholesterol levels are often not very elevated but the LDL particles tend to be small and dense. Thus the LDL-C concentration may be misleading as there will be more LDL particles for any given cholesterol concentration. Measuring apolipoproteinB (apoB) reflects the total number of atherogenic lipid particles. Non-HDL-C (calculated as TC-HDLC) reflects all cholesterol carried in atherogenic lipid particles and provides similar, but not identical, information to apoB measurements.

Although elevated LDL-C is not the major lipid abnormality in patients with type 2 diabetes, clinical trials have clearly demonstrated that reduction of LDL-C particularly with statin treatment reduces the risk for major cardiovascular events[9] (Level A).

Patients with poorly controlled type 1 diabetes often have elevated triglyceride and, to a lesser extent, cholesterol levels. In well-controlled patients, the levels of total cholesterol, triglycerides and LDL cholesterol are similar to those of non-diabetic individuals. Individuals with diabetic renal disease, both microalbuminuria and frank proteinuria, have higher total cholesterol, LDL cholesterol and triglyceride levels, and lower HDL cholesterol levels.

16.4.1 Goals of therapy

LDL-C is the primary target of lipid-lowering therapy. The focus on LDL-C is supported by results of large, controlled clinical trials that have demonstrated that LDL-C lowering with statins will reduce the risk of major cardiovascular events and reduce all-cause mortality. Importantly the benefits of statin therapy are independent of the baseline LDL-C value. Although lowering triglycerides, as a surrogate for remnant lipoprotein cholesterol, and increasing HDL-C are both intuitively appealing and biologically plausible interventions clinical trials thus far (nicotinic acid, fibrates, cholesterol ester transfer protein inhibitors) have failed to demonstrate cardiovascular event rate reductions. Further research is ongoing in this area.

The ideal lipid profile of a patient with diabetes is:

Total cholesterol	< 4.5 mmol/l
LDL cholesterol	< 1.8 mmol/l
HDL cholesterol	> 1.0 mmol/l in men, and
	> 1.2 mmol/l in women
Triglycerides	< 1.7 mmol/l

16.4.2 Monitoring serum lipids

At the first visit, the total cholesterol and triglyceride levels should be checked. If either is elevated, a fasting lipogram (10 hour fast) should be performed (i.e. total cholesterol, triglycerides, HDL cholesterol and calculated LDL cholesterol). If the laboratory is able to measure LDL-C directly it is not essential for patients to fast, but the non-fasting state should be taken into account when interpreting triglyceride levels. In patients with hypertriglyceridaemia triglycerides may vary markedly according to the composition and timing of the last meal and fasting triglycerides are best for serial comparisons. If the results of the fasting lipogram are satisfactory, this test should be repeated annually. If the levels are unsatisfactory, the test should be repeated in three months, after the patient has been following an appropriate lipid-lowering diabetic diet, weight reduction has been encouraged, glucose control has been established, and lipid-lowering therapy has been instituted, or the dose of lipid-lowering therapy has been adjusted.

16.4.3 Nonpharmacological therapy

Diet is the cornerstone of therapy. Severe hypertriglyceridaemia (TG > 10 – 15 mmol/L) usually responds particularly well to dietary triglyceride restriction. All diabetic patients should receive standard advice on healthy eating habits and preferred food choices as also discussed in the chapter on medical nutrition therapy.

Calories: The calorie content of the diet must be adjusted to achieve ideal body weight. Even moderate weight loss (e.g. 5-10%) can be of great value in improving dyslipidaemia and glycaemia.

Fats: There is limited evidence on the ideal macronutrient composition of the diet in patients with diabetes. The type of fat consumed is probably more important than the total amount of fat in patients without severe hypertriglyceridaemia. Mediterranean style diets high in monounsaturated fatty acids have been shown to improve glycemic control, lipid parameters and outcomes in patients with type 2 diabetes. Trans fats should be avoided because of their proven negative effect on cardiovascular outcomes, while saturated fat intake should be limited to less than 7% of total caloric intake. The consumption of oily fish should be encouraged. Routine prescription of omega-3 supplements for the primary or secondary prevention of cardiovascular disease is not supported by randomised controlled trials. Omega-3 supplements in sufficiently high doses (2-4 g/day) can decrease moderately elevated triglycerides.

Fibre: The fibre content of the diet should be increased aiming for an intake of around 14 g per 1000 kcal consumed.

Alcohol: In the presence of obesity and/or hypertriglyceridaemia, alcohol should be avoided. Otherwise, alcohol should be restricted to maximally one (in females) or two (in males) units per day.

Poor metabolic control is a contributor to diabetic dyslipidaemia, and it is important to ensure that the glycaemic control is adequate. Adequate glycaemic control is particularly

important in patients with severe hypertriglyceridaemia (TG>10 -15 mmol/L) where it is the most common secondary precipitating factor.[10] In patients with severe hypertriglyceridaemia and poorly controlled diabetes initiation or intensification of insulin therapy should not be delayed.

Secondary causes of hyperlipidaemia (e.g. hypothyroidism, renal disease, medications [corticosteroids, retinoic acid derivatives, protease inhibitors, oestrogen, sirolimus and others] and alcohol abuse) must always be excluded.

16.4.4 Pharmacological therapy

- Achieving the recommended LDL-cholesterol level is the primary goal of therapy. Statins are the first-line agents for lowering LDL cholesterol in patients with diabetes. In patients unable to achieve LDL cholesterol goals on the maximum dose of a highly potent statin (i.e. atorvastatin or rosuvastatin), or in those unable to tolerate a sufficiently potent statin dose, combination therapy of a statin with ezetimibe should be considered. There is now also outcome evidence for the clinical utility of statin + ezetimibe combinations from the recently published IMPROVE-IT trial.[11]
- The addition of a fibrate or another triglyceride-lowering drug may be considered if triglyceride levels remain > 2 mmol/l, but only after reaching the LDL-cholesterol target with a statin. However, ideally these patients should be referred for specialist assessment as there is currently considerable uncertainty regarding optimal lipid management in diabetes beyond LDL cholesterol lowering. Clinical trials conducted to date do not support triglyceride reduction as a means to reduce CVD risk in diabetic subjects. Similarly there is little evidence to show that raising HDL-C with drug therapy reduces cardiovascular risk.
- Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for all patients with type 2 diabetes who:
  - Have existing cardiovascular disease (i.e. ischaemic heart disease, cerebrovascular disease or peripheral vascular disease).
  - Have chronic kidney disease (eGFR < 60 ml/minute/1.73m^2).
  - Are either older than 40 years of age or have had diabetes for longer than 10 years, with one or more additional cardiovascular risk factor, i.e. hypertension, cigarette smoker, low HDL-cholesterol level, family history of early coronary heart disease, and any albuminuria.
- Drug interactions should always be considered when prescribing a statin. For example, simvastatin should not be co-prescribed with most antiretroviral agents, and only low doses of simvastatin should be used with calcium-channel blockers. Simvastatin 80 mg/day should not be newly initiated in any patients.[12]
- In diabetic patients at lower risk (i.e. those without established cardiovascular disease or chronic kidney disease, or those younger than 40 years of age or who have diabetes of less than 10 years' duration without additional cardiovascular risk factors), a targeted approach should be followed. Statin therapy should be considered if the LDL cholesterol is > 1.8 mmol/l.
- Specialist referral should occur when triglyceride levels are > 5 mmol/l in the controlled diabetic, or > 15 mmol/l before treatment.

16.4.4.1 ***HMG-CoA reductase inhibitors or Statins*** *(e.g. simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin):* The statins are powerful cholesterol-lowering agents and are generally the lipid-lowering therapy of choice in diabetics. Statins lower serum cholesterol by 16-65%. Statin treatment in type 2 diabetes has been shown to markedly reduce the risk of cardiovascular events and improve survival. Statins do not fully address all the abnormalities found in diabetic dyslipidaemia (low HDL cholesterol and high triglycerides) but their use is supported by extensive safety and efficacy data.[9] Statins are safe in renal failure.

16.4.4.2 ***Fibric acid derivatives*** *(e.g. bezafibrate, fenofibrate, gemfibrozil):* Fibrates are indicated when there is severe hypertriglyceridaemia (> 10-15 mmol/l) to reduce the risk of acute pancreatitis. Combination therapy with statins in those with moderate hypertriglyceridaemia, low HDL cholesterol and adequately controlled LDL cholesterol has intuitive appeal but lacks a definite evidence base. Specialist consultation is advised before initiating a statin + fibrate combination. Fibrate doses must be reduced in patients with renal failure. Gemfibrozil should not be used in combination with a statin.

16.4.4.3 ***Cholesterol absorption inhibitors***: Ezetimibe is a selective inhibitor of cholesterol uptake by the gastrointestinal tract. Ezetimibe lowers LDL cholesterol by 15-20%, and can be used in combination with statin therapy if LDL-cholesterol goals are not achieved with statin therapy alone.

16.4.4.4 ***Bile acid sequestrants*** *(e.g. cholestyramine):* Bile acid sequestrants should be used with caution in the management of diabetic dyslipidaemia, as they can worsen hypertriglyceridaemia (especially if the baseline triglycerides are elevated) which may secondarily lower HDL-cholesterol levels.

16.4.4.5 ***Niacin:*** lowers triglycerides, lipoprotein(a), LDL cholesterol and increases HDL cholesterol. Niacin administration at higher doses leads to flushing as well as gout and can raise blood glucose; adjustments to treatment of dysglycaemia may be required. Niacinamide (nicotinamide) does not result in flushing but does not lower cholesterol. Trial evidence does not support the use of niacin for cardiovascular risk reduction in diabetic subjects.

16.4.4.6 ***Newer therapies***: The role of proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitor therapy, microsomal triacylglycerol transfer protein (MTP)

inhibitor or cholesterol ester transfer protein (CETP) inhibitor therapy for the management of diabetic dyslipidaemia remains uncertain. These agents may have a role in the future if they are found to reduce cardiovascular risk in diabetic patients.

Authors: Derick J Raal, Dirk J Blom and Adrian D Marais

Editors: Aslam Amod and Nazeer A Mohamed

References

1. The Emerging Risk Factors Collaboration. Association of cardiometabolic multimorbidity with mortality. JAMA 2015;314(1): 52-60
2. Low Wang CC, Hess CN, Hiatt WR. et al. Clinical Update. Cardiovascular disease in diabetes mellitus. Circulation 2016;133:2459-2502
3. Mazzone T, Chait A, Plutzky J. Cardiovascular disease in type 2 diabetes mellitus: insights from mechanistic studies. Lancet 2008:371:1800-1809.
4. Task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2011;32(14):1769-1818.
5. Garder AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm -2016 Executive Summary. Endocrine Practice 2016;22(1): 84-113
6. Fox CS, Golden SH, Anderson C, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence. A scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2015;38:1777-1803
7. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome. Circulation. 2009;120:1640-1645.
8. Shah RV, Goldfine AB. Statins and risk for new-onset diabetes mellitus. Circulation 2012;121:e282-284.
9. Cholesterol Treatment Trialists' (CTT) collaborators. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371:117-125.
10. Hogue JC, Lamarche B, Tremblay AJ, et al. Evidence of increased secretion of apolipoprotein B-48-containing lipoproteins in subjects with type 2 diabetes. J Lipid Res 2007;48:1336-1342
11. Cannon CP, Blazing MA, Giugliano AP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372:2387-2397
12. Egan A, Colman E. Weighing the benefits of high-dose simvastatin against the risk of myopathy. N Engl J Med. 2011;364(4): 285-287.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 17: Aspirin therapy for type 2 diabetes

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Aspirin is currently not recommended for the primary prevention of cardiovascular disease in patients with diabetes mellitus (who have not yet had a cardiovascular event).	B
Aspirin is strongly recommended for the secondary prevention of cardiovascular disease in type 2 diabetes.	A
The optimal aspirin dose for secondary prevention is not known. SEMDSA endorses the 2011 Canadian Cardiovascular Society Guidelines recommendation to use 75 mg to 162 mg of regular aspirin per day.	C
Patients with established cardiovascular disease who are intolerant to aspirin should be offered an alternative platelet aggregation inhibitor.	C
Improved vascular protection is more effectively achieved with inhibition of the renin-angiotensin-aldosterone system and lipid modifying therapies.	A

Primary prevention

Individuals with type I and type 2 diabetes mellitus are recognized to have accelerated cardiovascular age approximately 10 to 15 years in advance of the chronological age.[1] The management of diabetes mellitus seeks to address the consequent reduction in life expectancy evident in these individuals[2] by addressing both behaviour and using targeted pharmacological therapies. The evidence for the use of aspirin in primary prevention of cardiovascular disease is lacking despite *in vitro* evidence of increased platelet aggregation that might be expected to benefit from platelet inhibition with aspirin. Tests in patients with diabetes suggest that platelets may be more resistant to the inhibitory effects of aspirin.[3]

Numerous studies have suggested that in the general population aspirin reduces non-fatal myocardial infarction in men who have no previous history of cardiovascular disease, but this data cannot be extrapolated to women. Prior to the Women's Health Study (WHS) published in 2005, of the 5 trials addressing the primary prevention of cardiovascular disease with aspirin, 3 had been trials which exclusively assessed men. The WHS concluded that the use of aspirin for primary prevention in women resulted in a reduction of stroke risk without altering the risk of myocardial infarction or death from cardiovascular causes.[4] The Antithrombotic Trialists' meta-analysis reviewed 95, randomized trials of antiplatelet therapy that had been published up to 1997, including only 5000 individuals with diabetes in 9 of the trials; when high risk subjects without diabetes were compared to subjects with diabetes, it was not possible to show any significant benefit in the subjects with diabetes.[5]

Specific primary prevention trials focusing on patients with type 2 diabetes, including the Early Treatment of Diabetic Retinopathy Study, the Japanese Prevention of Atherosclerosis with Aspirin in Diabetes Trial and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) Trial have failed to show any clinically significant benefits for mortality, myocardial infarction or stroke.[6-8]

Conversely, aspirin use increases the risk of gastrointestinal bleeding by 50% to 70% regardless of dose or formulation; this risk may be increased in individuals with diabetes but also individuals > 70 years of age.[9]

The National Institute for Health and Care Excellence (NICE) in the UK performed a risk benefit analysis for aspirin use in type 2 diabetes in 2015 and found possible marginal benefits for primary cardiovascular disease prevention, but the risk of harm was excessive.[10] NICE has issued a strong recommendation that aspirin not be offered to patients with type 2 diabetes for primary prevention. Other anti-platelet agents are also not recommended for primary prevention.

The ASCEND trial (A Study of Cardiovascular Events in Diabetes) and the ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes) are currently ongoing and may give clarity to this issue in the next year or two. In the meantime, SEMDSA endorses and adopts the NICE recommendations for primary prevention.

Secondary prevention

The benefits of aspirin therapy for secondary prevention of cardiovascular disease in patients with diabetes are well established and there has been no change to the recommendation of aspirin for type 2 diabetes mellitus and established cardiovascular risk, provided there is no contraindication to its use. Clopidogrel may offer benefit to individuals with intolerance to aspirin.[11]

Aspirin dosage and formulation

Numerous studies have used aspirin both for primary and secondary prevention in varying doses from 30-600 mg. There is no randomised controlled trial which proves the benefits of doses of 75-162 mg of daily aspirin. However, these doses are better tolerated and as effective as higher doses in preventing cardiovascular events. In addition lower doses are associated with fewer events of bleeding.[11,12] The increased risk for gastrointestinal haemorrhage applies to both primary and secondary prevention.[9]

The risk of upper gastrointestinal bleeding may not be reduced by the use of enteric coated or buffered formulations.[13,14] When platelet turnover is rapid as in diabetic vascular disease, the steady plasma aspirin concentration from enteric-coated aspirin may theoretically allow for more constant thromboxane synthesis suppression.[15] "Aspirin Resistance" has been described in diabetic patients using a variety of methods of measurement,[16] but other studies have not shown this to be the case.[17] One trial suggested that a more frequent dosing schedule of aspirin may reduce platelet reactivity in diabetic patients,[18] but these observations alone are insufficient to empirically recommend higher doses at this time.[19]

Authors: Hilton Kaplan and Tanya Kinvig
Editors: Aslam Amod and Zaheer Bayat

References

1. Booth GL, Kapral Mk, Fung K, TU JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet 2006; 368:29-36
2. Manuel DG, Schultz SE. Health related quality-of-life and health adjusted life expectancy of people with diabetes in Ontario, Canada 1996-1997. Diabetes Care 2004; 27:407-14
3. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Influence of aspirin resistance on platelet function profiles in patients on long-term aspirin and Apidra grew after percutaneous coronary intervention. Am J Cardiol 2006; 97:38-43
4. Ridker PM, Cook NR, Lee IM et al. A randomised trial of low dose aspirin for primary prevention of cardiovascular disease in women. N Engl J Med 2005; 352:1293-304
5. Collaborative overview of randomised trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ 1994; 308:81-106
6. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. JAMA 1992; 268:1292-300
7. Ogawa H, Nakayama M, Morimoto T, et al. Low dose aspirin for primary prevention of atherosclerotic events in patients with type II diabetes: a randomised controlled trial. JAMA 2008; 300:2134-41
8. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo-controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BM J 2008; 337: a1840.
9. Derry S, Loke YK. Risk of gastrointestinal haemorrhage was long term use of aspirin: meta-analysis. BMJ 2000; 321:1183-7
10. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management. NICE Guideline [NG28]. 2015. https://www.nice.org.uk/guidance/ng28. Accessed January 28, 2016.
11. Bell AD, Roussin A, Cartier R, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society guidelines. Can J Cardiol 2011; 27 (suppl A): S1-59
12. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002; 106 (3) 388-91
13. Risk of upper gastrointestinal bleeding and perforation associate with low-dose aspirin as plain and enteric coated formulations: De Abajo F.J, Rodrguez L.A.G. BMC Pharmacology 2001 1:1
14. Kelly J.P, Kaufman D.W., Jurgelon J.M. et al : Risk of aspirin associated major upper gastrointestinal bleeding with enteric coated or buffered product. Lancet 1996,348:1413-1416
15. Aspirin Therapy in Diabetes; American Diabetes association; Diabetes Care 2003 Jan;26(suppl 1): s87-s88
16. Larsen S.b, Grove E.L., Neergard-Petersen S, Wurtz M, Hvas A-M, Kristensen S.D. Determinants of reduced antiplatelet effects of aspirin in patients with stable coronary artery disese. PLoS One 2015;10:e0126767
17. Zaccardi F, Rizzi A,Petrucci,G, et al.In vivo platelet activation and aspirin responsiveness in type 1 diabetes. Diabetes 2016;65:503-509 93.
18. Bethel M.A, Harrison P, Sourij H, et al. Randomized controlled trial comparing impact on platelet reactivity of twice-daily with once-daily
19. Standards of Medical Care in Diabetes. American Diabetes Association. January 2017

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Chapter 18: Hypertension in Type 2 Diabetes Mellitus

SEMDSA Type 2 Diabetes Guideline Expert Committee

SEMDSA 2017 Recommendations	
Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have their blood pressure confirmed on a separate day.	B
Threshold for initiating treatment of blood pressure in type 2 diabetes is >140/90 mmHg.	B
Systolic blood pressure treatment target for most patients is between 130 and 140 mmHg.	A
Diastolic blood pressure treatment target for most patients is between 80 and 90 mmHg.	A
Systolic blood pressure treatment target for patients at high risk for stroke is below 130 mmHg if this can be achieved without undue treatment burden.	A
Lifestyle intervention consisting of weight loss (if overweight or obese), reducing sodium intake, moderation of alcohol intake and increased physical activity should be encouraged in all patients diagnosed with hypertension.	B
All classes of antihypertensive drugs are efficient in reducing all cause and cardiovascular mortality.	A
Combination therapy with an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) is not recommended for primary care.	C
In patients with type 2 diabetes and hypertension, indapamide (thiazide-like) is the preferred diuretic.	A
For patients with type 2 diabetes without albuminuria, an ACE-inhibitor, ARB, thiazide-like diuretic or calcium channel blocker (CCB) are suitable first choices for monotherapy. Diuretics or CCBs are the preferred initial treatment in Black patients.	C
Compelling Indications for drug classes	
The following classes of drugs have been shown to have benefit in diabetic kidney disease: ACE-inhibitors, ARBs, thiazide-like diuretics (indapamide) and non-dihydropyridine CCBs (verapamil or diltiazem).	A
For patients with heart failure, an ACE-inhibitor or ARB and indapamide is preferred. Calcium channel blockers are not recommended.	A
For patients at high risk for stroke (e.g. history of previous cerebral ischaemia, significant carotid stenosis, uncontrolled hypertension), calcium channel blockers are recommended and beta blockers should be avoided.	B
For patients with coronary artery disease, ß-blockers are indicated.	A

18.1 Introduction

Systemic hypertension is common in type 2 diabetes mellitus and will affect the majority of patients at some point in the course of their disease. People with type 2 diabetes mellitus are at a greater risk than non-diabetics for developing hypertension[1] and are more likely to develop target organ damage.[2] The development and progression of organ damage due to hypertension in diabetes appears to differ from that for the non-diabetic population.

Hypertension is an important modifiable risk factor for micro- and macrovascular disease. Blood pressure (BP) must be measured at every clinic visit, after the patient has been seated and has rested for at least five minutes. It is essential to use an appropriately sized cuff, as small cuffs will yield falsely elevated pressure readings. Measure the BP in both arms at the initial consultation, and thereafter in the arm with the higher BP. The systolic BP should first be estimated by palpation and then by auscultation, to avoid missing the auscultatory gap. The diagnosis of hypertension is confirmed if the BP remains > 140/90 mmHg on two separate days.

18.2 Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) is determined using a device worn by the patient over a period of 24 to 48 hours and measures blood pressure at regular intervals, usually

every 15 to 20 minutes.[3] The device records all the blood pressure readings taken during this time period. If full 24 hour readings cannot be obtained then six to eight hours of ABPM may be adequate.[4] From this, the average day and night blood pressures can be determined. When using ABPM, hypertension is defined as a 24-hour average blood pressure greater than or equal to 130/80 mmHg.[5]

While ABPM is not available in most clinicians' offices, it is considered to be the gold standard for the diagnosis of hypertension. When compared with ABPM, the sensitivity and specificity of office-based BP measurements are poor (75% for both).[6]

Indications for measuring ABPM:[7,8,9]

- Suspected white coat hypertension
- Hypertension resistant to increasing medications
- Hypotensive symptoms while taking antihypertensive medications
- Autonomic dysfunction
- Suspected episodic hypertension (eg, phaeochromocytoma).

18.3 Thresholds for pharmacological treatment of blood pressure (BP)

The benefit of lowering blood pressure was initially shown by the Blood Pressure Lowering Treatment Trialists Collaboration. This analysis showed that a modest drop of 6.4 mmHg of Systolic Blood Pressure was associated with a decrease in stroke, cardiovascular disease and total mortality.[10]

Two large meta-analyses have shown that treatment of a systolic blood pressure of greater than or equal to 140 mmHg results in more benefit than harm.[11,12] In the Brunström meta-analysis,[11] 49 trials (73 738 participants) were included while in the Emdin meta-analysis,40 trials judged to be of low risk of bias (100 354 participants) were included.[12] Given the slightly different weighting of trials in the two meta-analyses, the findings of benefit and harm of various organ systems differ slightly but the threshold for initiating treatment remains constant.

In the Brunström meta-analysis if the baseline BP was greater than 150 mmHg, antihypertensive treatment reduced the risk of all-cause mortality, cardiovascular mortality, myocardial infarction, stroke and end stage renal disease. If baseline systolic blood pressure was between 140 and 150 mm Hg, additional treatment reduced the risk of all-cause mortality, myocardial infarction and heart failure. If baseline systolic blood pressure was less than 140 mm Hg, further treatment increased the risk of cardiovascular mortality with a tendency towards an increased risk of all-cause mortality.[11] The Emdin meta-analysis showed that each 10 mmHg reduction of systolic blood pressure was associated with significantly lower risk of mortality, cardiovascular events, coronary heart disease, stroke, albuminuria, and retinopathy. However, when trials were stratified by mean baseline SBP greater than or equal to 140 mmHg or less than 140 mmHg, blood pressure–lowering treatment was associated with lower risks of stroke and albuminuria, regardless of initial systolic blood pressure.[12]

18.4 Targets for pharmacological treatment

The Brunström meta–analysis specifically focused on the evidence for positive or negative outcomes for attained systolic BP's in clinical trials.[11] The following outcomes were observed:

- The all-cause mortality reduction observed with treatment at a threshold of 140 mmHg was lost when the BP was lowered below 130 mmHg.
- Trend towards harm for CV mortality was observed when the BP was lowered to below 130 mmHg.
- The myocardial infarction threshold for harm was at 132 mmHg.
- Stroke benefit was achieved only with a BP below 130 mmHg.
- Heart failure was reduced for an achieved BP between 130-140 mm Hg but this benefit was lost if the BP dipped below 130 mmHg.
- End-stage renal disease appeared to only be reduced if the pre-treatment BP was >150 mmHg and was treated to between 140 and 150 mmHg.
- Albuminuria was reduced by 29% if the BP was reduced to <140 but >130 mmHg and by 14% if the BP was dropped below 130 mmHg. The risk for retinopathy did not appear to be reduced significantly with BP lowering.

Diastolic BP targets for benefit and risk for harm were assessed by the Brunström analysis. Threshold for treatment appeared to be 90 mmHg and a 28% increase in CV mortality was noted for each 10 mmHg drop in BP below a threshold of 78 mmHg.

18.5 Compelling indication for the use of specific antihypertensives

In the Emdin review,all classes of antihypertensive drugs appeared to be efficient in reducing all cause and cardiovascular mortality, a finding supported by other researchers.[12,13] Heart failure was significantly reduced by angiotensin receptor blockers and diuretics (17% reduction), but increased by calcium channel blockers (CCB). CCBs were however associated with a lower risk of stroke and beta-blockers with a higher risk of stroke.

A recent review of angiotensin system blockers compared to active comparators showed no extra benefit other than a reduction of heart failure when compared to CCBs.[14]

Within the class of diuretics, thiazide–type (TT) and thiazide-like (TL) drugs must be specified. A meta-analysis of these drugs looking at outcomes of CV events and mortality as well as BP control, clearly showed a difference with a 12% reduction of CV events and 21% less heart failure with TL compared with TT drugs.[15] A further meta-analysis of head to head comparisons of hydrochlorothiazide (HCTZ) with indapamide (INDAP) and chlorthalidone confirmed that INDAP was more potent than HCTZ with a 54% greater BP reduction at comparable doses, without greater metabolic side effects.[16] The duration of action of INDAP was found to be >24-36 hours depending on the formulation, compared to the 12-16 hour effect of HCTZ.

INDAP was also noted to reduce left ventricular mass by 17%, more than that of enalapril, and was comparable to captopril and enalapril in reducing albuminuria in diabetic subjects. HCTZ has neither of these effects. Not specific to diabetes, indapamide has been shown to not have an adverse effect on serum lipids. Due to its widespread availability, and low cost, indapamide is considered to be the diuretic of choice in the management diabetic patients with hypertension.

The non- dihydropyridine CCBs, (verapamil and diltiazem) have been shown to have significant antiproteinuric effects in diabetic kidney disease.[17] The dihydropyridine CCBs (amlodipine and nifedipine) have been shown to have no consistent effect on protein excretion.

There is currently limited data regarding the potential benefits of combining therapy with ACE inhibitors and ARBs. While several small studies have shown an additive antiproteinuric effect when these drugs were used in combination, these finding were not reproducible in all studies. In the COOPERATE study (randomised controlled trial in non-diabetic renal disease), combination therapy with ACE inhibitors and ARBs was shown to be more effective that either drug alone in slowing the decline of GFR.[18] Until additional information and data for combination use in diabetes is made available, the use of either an ACE inhibitor or an ARB is recommended, rather than the combination of both classes.

Most patients with diabetes and hypertension require multiple-drug therapies to reach target blood pressure treatment goals. If the blood pressure remains uncontrolled, despite confirmed adherence of at least three antihypertensive agents of different classes (at optimal doses), the clinician should consider evaluation for secondary causes of hypertension.

Authors: Susan L. Brown and Zaheer Bayat
Editor: Aslam Amod

References

1. Williams B. Blood pressure and Diabetes: a fatal attraction. Eur Heart J. 2013;(44):3395-3397
2. Stamler J , Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention trial. Diabetes Care. 1993;16:434-44
3. Pickering TG, Miller NH, Ogedegbe G, et al. Call to action on use and reimbursement for home blood pressure monitoring: executive summary: a joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. Hypertension 2008; 52:1.
4. Wolak T, Wilk L, Paran E, et al. Is it possible to shorten ambulatory blood pressure monitoring? J Clin Hypertens (Greenwich) 2013; 15:570.
5. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens 2013; 31:1731.
6. Hodgkinson J, Mant J, Martin U, et al. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review. BMJ 2011; 342:d3621.
7. Hemmelgarn BR, McAllister FA, Myers MG, et al. The 2005 Canadian Hypertension Education Program recommendations for the management of hypertension: part 1- blood pressure measurement, diagnosis and assessment of risk. Can J Cardiol 2005; 21:645.
8. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens 2014; 32:3.
9. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013; 31:1281.
10. Turnbull F, Neal B, Algert C et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005 Jun 27; 165(12):1410-1419
11. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta analyses. BMJ 2016;352:i717 http.//dx.doi.org/10.1136/bmj.i717
12. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood Pressure lowering in Type 2 Diabetes A Systematic Review and Meta-analysis. JAMA. 2015;313(6):603-615
13. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analys. www.the lancet.com published on line December 23, 2015 http://dx.doi.org/10.1016/s0140-6736(15)01225-8
14. Bangalore S, Fakheri R, Toklu B, Messerli. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. BMJ 2016;352:i438
15. Olde Engberink RHG, Frenkel WJ, van den Bogaard B, Brewster LM, Vogt L, van den Born BH. Effects of thiazide-type and thiazide like diuretics on cardiovascular events and mortality systematic review and meta-analysis. Hypertension. 2015;65:1033-1040
16. Roush G, Ernst ME, Kostis JB, Tandon S, Sica DA. Head –to- head comparisons of Hydrochlorothiazide with Indapamide and Chlorthalidone Antihypertensive and Metabolic Effects. Hypertension. 2015;65:1041-1046
17. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med. 2008;148(1):30
18. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T: Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. Lancet. 361:117-124, 2003

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 19: Diabetic Kidney Disease

SEMDSA Type 2 Diabetes Guideline Expert Committee

SEMDSA 2017 Recommendations	
In adults, screening for CKD in diabetes should be conducted using a random urine ACR and a serum creatinine converted into an eGFR.	C
Screening should commence at diagnosis of diabetes in individuals with type 2 diabetes and repeated yearly thereafter.	C
A diagnosis of CKD should be made in patients with a random urine ACR ≥ 2.0 mg/mmol and/or an eGFR < 60 mL/min on at least two of three samples over a three month period.	C
All patients with diabetes and CKD should receive a comprehensive, multifaceted approach to reduce cardiovascular risk.	A
Adults with diabetes and CKD with either hypertension or albuminuria should receive an ACE inhibitor or an ARB to delay progression of CKD.	A
People with diabetes on an ACE inhibitor or an ARB should have their serum creatinine and potassium levels checked at baseline and within one to two weeks of initiation or titration of therapy and during times of acute illness.	C
Adults with diabetes and CKD should be given a "sick day" medication list that outlines which medications should be withheld during times of acute illness.	C
Combination of agents that block the renin-angiotensin-aldosterone system (ACE inhibitor, ARB, DRI) should **not** be routinely used in the management of diabetes and CKD.	A
Doses of anti-diabetic drugs may require adjustment as renal function declines.	C
People with diabetes should be referred to a nephrologist or endocrinologist with an expertise in CKD in the following situations: a. Chronic, progressive loss of kidney function b. ACR persistently >60 mg/mmol c. eGFR<30 mL/min d. Unable to remain on renal-protective therapies due to adverse effects such as hyperkalaemia or >30% increase in serum creatinine within 3 months of starting an ACE inhibitor or ARB e. Unable to achieve target BP (could be referred to any specialist in hypertension).	C

Abbreviations:
ACE, angiotensin-converting enzyme; ACR, albumin-to-creatinine ratio;
ARB, angiotensin II receptor block; CKD, chronic kidney disease; DRI, direct renin inhibitor.

19.1 Introduction

Chronic kidney disease (CKD) is defined as the presence of kidney damage (usually detected as urinary albumin excretion of ≥30 mg/day, or equivalent) **or** decreased kidney function (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) **for three or more months**, irrespective of the cause.[1] The persistence of the damage or decreased function for at least three months is necessary to distinguish CKD from acute kidney injury (AKI). Kidney disease attributable to diabetes is referred to as diabetic kidney disease (DKD).[2]

In South Africa, hypertension and type 2 diabetes are the dominant diseases associated with kidney failure, particularly in black ethnic groups.[3] Hypertension and other common chronic kidney diseases may also contribute to the aetiology of chronic kidney disease (CKD) in diabetic patients. In Africa, the overall prevalence of CKD in patients with diabetes varied from 11% in Tunisia to 83.7% in Tanzania.[4] The prevalence of DKD in South Africa is 14-16%[5] and 30.4% of patients on renal replacement therapy have diabetes.[6]

19.2 Identification and monitoring of diabetic kidney disease

Albumin excretion (albuminuria) and glomerular filtration rate (GFR) are both required to diagnose and monitor DKD.

19.2.1 Screening for albuminuria

Albumin excretion is an indicator of kidney damage in DKD.[2] Classic DKD progresses from subclinical disease to the earliest clinically detectable stage, which is characterised by persistent proteinuria (Figure I).[7,8] The rate of progression from normal albuminuria to moderately increased albuminuria, then to severely increased albuminuria is usually slow and it may take 5 years or longer to progress through each albuminuria stage (Table I). During the advanced overt proteinuria phase, the rate of decline of renal function can accelerate.[7] Risk factors for DKD include long duration of diabetes, poor glycaemic control, hypertension, male gender, obesity and cigarette smoking.[7] Apart from predicting DKD, moderately increased albuminuria (formerly known as microalbuminuria) is also a marker of cardiovascular disease risk.[9]

There is considerable intra-individual variation in daily albumin excretion necessitating the collection and testing of more than one specimen.[2] Daily albumin excretion may be increased by episodic hyperglycaemia, high blood pressure, high protein diet, fever, exercise, urinary tract infection and heart failure.[2] Moderately increased albuminuria (albumin excretion between 30-300 mg/day) is potentially reversible by treating raised blood pressure, plasma glucose and serum lipid levels to target in patients with type 1 diabetes,[10] and by administering drugs that inhibit the renin angiotensin aldosterone system (RAAS) in patients with type 2 diabetes.[1,11]

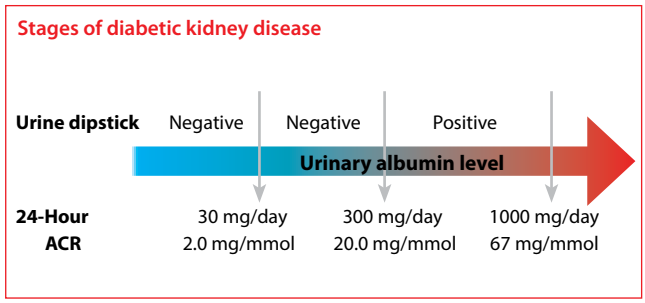


Figure I. Level of urinary albumin by various test methods and stage of diabetic kidney disease. ACR, urine albumin-to-creatinine ratio. Adapted from.[7]

Table I. Classification of chronic kidney disease based upon albuminuria[1,7]

Albuminuria Stages	Qualitative description	AER (mg/day)	Urine ACR (mg/mmol)
1	Normal to mildly increased	< 30	< 2
2	Moderately increased	30 - 300	2-20
3	Severely increased (may be subdivided into nephrotic and non-nephrotic and for differential diagnosis, management, and risk prediction)	> 300	> 20

*Adapted from References.[1,7] Values are for urinary albumin, not total urinary protein, which will be greater than urinary albumin levels.

Table II. Classification of chronic kidney disease based upon glomerular filtration rate[1,7]

Stages of chronic kidney disease of all types		
GFR stages	**Qualitative description**	**Renal function (ml/min/1.73m²)**
1	Kidney damage - normal or high GFR	≥ 90
2	Kidney damage - mildly ↓ GFR	60 - 89
3a	Kidney damage – mildly to moderately ↓ GFR	45 - 59
3b	Kidney damage – moderately to severely ↓ GFR	30 - 44
4	Kidney damage - severely ↓ GFR	15 - 29
5	Kidney failure (or dialysis)	< 15

*Adapted from References[1,7]

Table III. Factors favouring the diagnosis of classical DKD or alternative renal diagnoses[2,7]

DKD vs. Alternative renal disease	
Favours DKD	**Favours alternative renal diagnosis**
Persistent albuminuria	Extreme proteinuria (>6 g/day)
Bland urinary sediment	Persistent haematuria (micro- or macroscopic) or active urinary sediment
Slow progression of disease	Rapidly falling eGFR
Low eGFR associated with overt proteinuria	Low eGFR with little or no proteinuria
Other complications of diabetes present	Other complications of diabetes (e.g. retinopathy) not present or relatively not as severe
Known duration of diabetes > 5 years	Known duration of diabetes < 5 years
	Refractory hypertension
	> 30% reduction in eGFR within 3 months after initiation of an ACE-inhibitor or an ARB
	Family history or non-diabetic renal disease (e.g. polycystic kidney disease)
	Signs or symptoms of systemic disease

19.2.2 Estimation of glomerular filtration rate

Glomerular filtration rate is used to quantify kidney function.[2] Estimated glomerular filtration rate (eGFR) is recommended to determine and monitor kidney function in DKD and other causes of CKD.[2] In spite of limitations, the Modification of Diet in Renal Disease Study Group (MDRD) formula[13] remains the preferred method of calculating eGFR.[2] This equation requires knowledge of the patient's age, sex, serum creatinine and race. The eGFR is particularly useful for assessing changes in renal function over prolonged periods but should not be used in situations where kidney function may be acutely compromised e.g. during dehydration. CKD can be conveniently staged according to eGFR (Table II).

19.3 Other kidney diseases in people with diabetes

Relying on albuminuria alone may be insufficient in identifying all patients with diabetes who have renal disease.[7] In a biopsy series it was found that hypertensive or ischaemic nephropathy was as common as diabetic glomerulosclerosis in patients with type 2 diabetes with evidence of chronic kidney disease (CKD).[14] Health care workers should be aware that other common diseases may be the cause of kidney disease in a patient with diabetes or that other diseases may co-exist in these patients. This is especially true in South Africa with its high burden of HIV and the potential for HIV-associated CKD.[3] The most important distinguishing features between DKD and other causes of CKD are shown in Table III. Additional testing and/or referral may be necessary to determine the cause of kidney disease in patients with diabetes exhibiting any of these features.

19.4 Screening recommendations

19.4.1 Precautions

Exclude transient causes of albuminuria (e.g. recent strenuous exercise, menstruation, fever, urinary tract infection, pregnancy, uncontrolled heart failure, acute severe elevation in blood pressure or blood glucose), low eGFR (e.g. dehydration, hypovolaemia), and acute renal failure on clinical grounds before each screening and urine dipstick testing.[7]

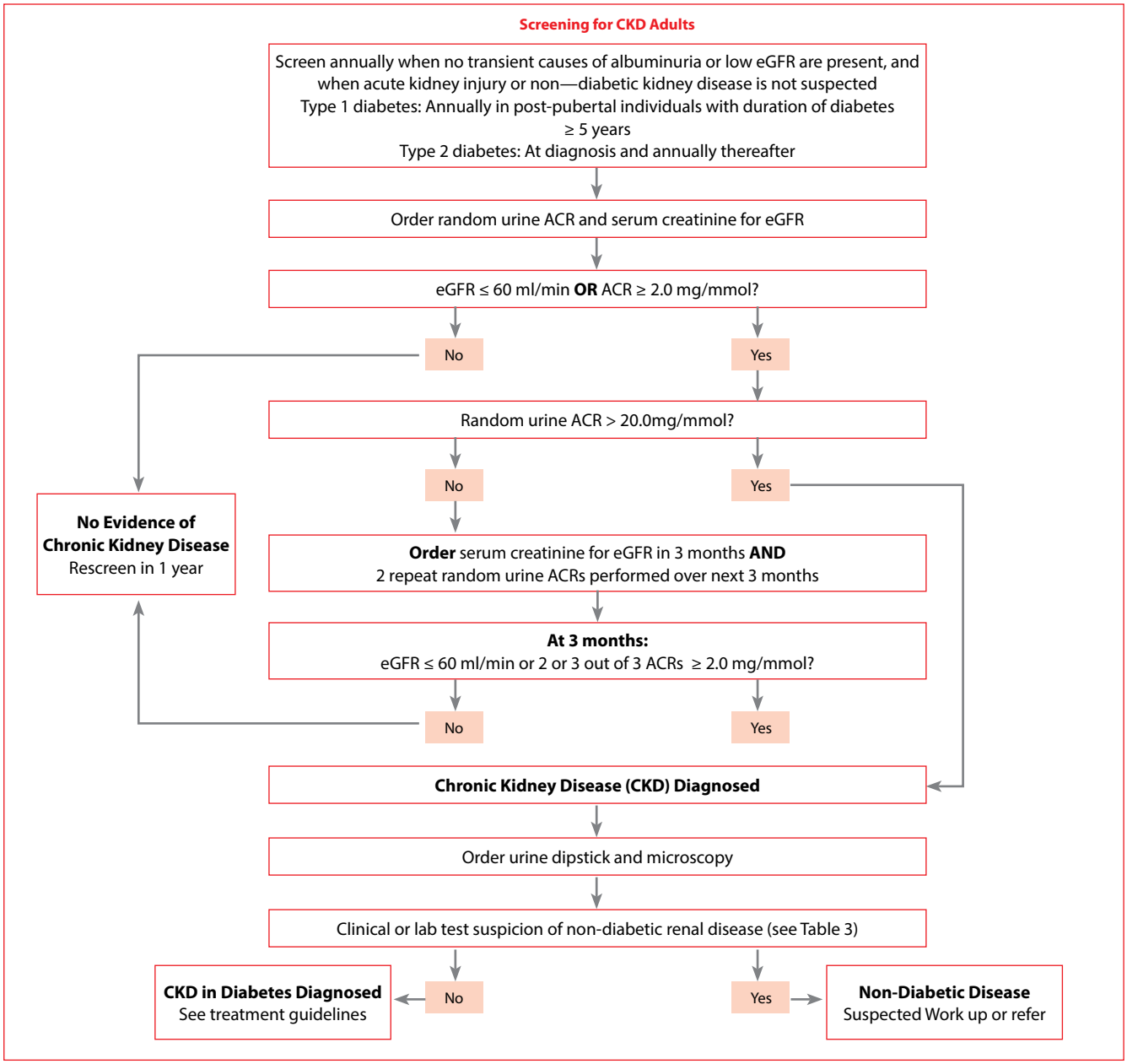


Figure II. Screening for chronic kidney disease (CKD) in people with diabetes. ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.[7]

19.4.2 Indications for screening

Annual screening for DKD is indicated in all post-pubertal people with type 1 diabetes 5 years after diagnosis, and in all people with type 2 diabetes at the time of diagnosis and annually thereafter.[7] Screening for CKD in people with diabetes should ideally be performed with the measurement of the albumin level in a first morning urine specimen and a serum creatinine measurement that is then converted into an eGFR and the result expressed as ACR[8] (Figure II). When a first morning urine specimen is inconvenient, an untimed "spot" urine sample is acceptable.[8]

An abnormal screening test should be confirmed by repeat testing of the eGFR within three months, and two more urine ACR measurements performed during that interval.[7,8] If either the eGFR remains low or at least two of the three random urine ACRs are abnormal, then a diagnosis of CKD is confirmed.[8] The exception to this approach is when the random urine ACR indicates albuminuria in the severely increased albuminuria range, as this level of proteinuria rarely resolves spontaneously, so confirmatory testing is usually unnecessary.[7]

Once a diagnosis of CKD has been made, a urine sample for dipstick and microscopy should be ordered.[7] In the absence of any significant abnormalities other than proteinuria, a presumptive diagnosis of kidney disease due to diabetes can be made. The presence of clinical or laboratory abnormalities suggesting nondiabetic kidney disease indicates the need for appropriate workup or referral.[7]

19.5 Prevention, treatment and follow up

19.5.1 Prevention

Tight blood sugar control in patients with type 1 diabetes reduces the risk of developing microvascular diabetes complications including DKD.[15] Tight blood sugar control comes at the risk of hypoglycaemia and there is no firm evidence for specific blood glucose targets. There is a lack of evidence from RCTs on the effects of tight blood sugar control in older patient populations or patients with macrovascular disease. Although tight blood glucose control in patients with type 2 diabetes reduces the risk of developing albuminuria, evidence is lacking in terms of a benefit for clinically important renal endpoints.[16,17] A recent Cochrane review concluded that angiotensin-converting enzyme inhibitors (ACEi) reduce the risk of new onset moderate and severe albuminuria with similar benefits in people with and without hypertension.[18] In this meta-analysis angiotensin receptor blocking agents (ARBs) were only of value in preventing kidney disease in high risk patients.

19.5.2 Treatment

Although intensive glycaemic control may slow down the progression of DKD in patients with type 2 diabetes,[16,20] lowering blood pressure is the most effective strategy in preventing end-stage renal disease in patients with established DKD.[21] Progression of DKD in patients with type 2 diabetes can be slowed down by the use of either an ACEi or an ARB.[22] Since ACE inhibitors have been shown to reduce major CVD events in patients with diabetes, and since the risk of CVD is increased in patients with albuminuria, ACE inhibitors should remain first-line agents in the treatment of patients with diabetes who have established albuminuria.[23]

Combination treatment with an ACEi and an ARB to prevent progression of DKD is not recommended on the grounds of increased risk of hyperkalaemia, and renal dysfunction.[24,25] A recent meta-analysis, however, showed that the most effective strategy to prevent end-stage kidney disease in patients with established DKD is by lowering blood pressure using dual treatment with an ARB and an ACEi,[26] while monotherapy with an ARB was also effective but less so than dual therapy.[21] Unfortunately, no blood pressure-lowering strategy prolonged survival in adults with diabetes and kidney disease.[26] Any benefits of combined ACE inhibitor and ARB treatment need to be balanced against potential harms of hyperkalaemia and acute kidney injury.[21,26] At this stage combination therapy with an ACE inhibitor plus an ARB should **not** be used in patients with DKD.

Initiation of an ACEi in patients with diabetes and serum creatinine levels greater than 124 µmol/L is associated with acute increases in serum creatinine of up to 30% that stabilises within the first two months of ACEi therapy and long-term preservation of renal function.[27] A significant increase in serum potassium and

Table V. Modifications of antidiabetic drugs in patients with type 2 diabetes mellitus

Class	Drug	Dosing recommendation stages 3 and 4 CKD or kidney transplant	Dosing recommendation dialysis
Second-generation Sulfonylureas	Glipizide, gliclazide	Preferred sulfonylurea No dose adjustment	Preferred sulfonylurea No dose adjustment
	Glibenclamide	Avoid	Avoid
	Glimepiride	Initiate at low dose, 1 mg/day	Avoid
Glucosidase inhibitors	Acarbose	Not recommended if serum creatinine >180 µmol/L	Avoid
Biguanides	Metformin	See text	Avoid
Meglitinides	Repaglinide	No dose adjustment	Avoid
	Nateglinide	Initiate at low dose (60 mg before each meal)	Avoid
Thiazolidinediones	Pioglitazone	No dose adjustment	No dose adjustment

Adapted from the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines).[3]

serum creatinine levels have been described in patients with bilateral renal artery stenosis within two weeks of initiation of a RAAS blocker.[28] For these reasons, the serum creatinine and potassium should be checked between one and two weeks after initiation or titration of a RAAS blocker.[7] For patients in whom a significant change in creatinine or potassium is seen, further testing should be performed to ensure that these results have stabilised.[7]

Any degree of albuminuria increases the risk of cardiovascular events in diabetic as well as in non-diabetic individuals.[29] Cardiovascular risk factors must be treated in all patients with CKD to address this risk. An intensified long-term intervention aimed at multiple risk factors in patients with type 2 diabetes and moderate albuminuria reduces the risk of cardiovascular and microvascular events by 50 percent.[30]

There are no randomised controlled trials of blood pressure levels in diabetes that have examined CKD events as outcomes. Blood pressure levels below 140/90 mmHg in diabetes are recommended to reduce CVD mortality and slow CKD progression (KDIGO, 2012). In individuals with albuminuria, consider lower blood pressure targets of < 130/80 mmHg.[20,21]

People with diabetes should be referred to a nephrologist or specialist physician with an expertise in CKD in the following situations:

a. Chronic, progressive loss of kidney function
b. ACR persistently >60 mg/mmol
c. eGFR<30 mL/min
d. Unable to remain on renal-protective therapies due to adverse effects such as hyperkalaemia or >30% increase in serum creatinine within 3 months of starting an ACE inhibitor or ARB
e. Unable to achieve target BP (could be referred to any specialist in hypertension).

19.6 Sick day rules

If patients become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g. due to gastrointestinal upset or dehydration), they should be instructed to withhold medications which will increase the risk for decline in kidney function or have reduced clearance and increased risk of adverse effects (Table IV).[7] Patients should be instructed that increased frequency of self-monitoring of blood glucose will be required and adjustments to their doses of insulin or oral anti-hyperglycaemic agents may be necessary.

Table IV. Medications that should be withheld or dose reduced during acute illness[7]

Analgesics
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
Direct renin inhibitors
Diuretics
Metformin
Non-steroidal anti-inflammatory agents
SGLT2-inhibitors
Sulfonylureas

19.7 Modifications of antidiabetic drugs in patients with type 2 diabetes mellitus[3]

Patients with stages 3-5 kidney disease are at increased risk of hypoglycaemia due to decreased renal clearance of insulin and sulfonylureas and also due to reduced gluconeogenesis. This has the following implications:

- In patients with type 1 diabetes, insulin needs may change with decreasing renal function, as CKD is associated with insulin resistance and there is decreased renal clearance of insulin with advancing CKD.
- Metformin should be used with caution in patients with stages 4 and 5 CKD. Its use in CKD carries a small risk of severe lactic acidosis; the risk increases with decreasing glomerular filtration rate (GFR) and the dose should be adjusted. The use of metformin should be reviewed when the patient reaches stage 3 CKD and its use is contraindicated in stages 4 and 5 CKD.
- Sulfonylureas: First-generation sulfonylureas should be avoided. Second-generation sulfonylureas may be used in patients who have learnt to avoid hypoglycaemic episodes, as long as their diabetes is controlled and nutritional status is satisfactory.
- Thiazolidinediones: These may be used in patients without heart failure. Caution is advised in patients with ischaemic heart disease.
- Insulin: When insulin therapy is used, care should be taken to avoid hypoglycaemic episodes, as the renal clearance of insulin declines with advancing renal impairment.
- DPP-4 antagonists (vildagliptin, saxagliptin) can be used with dose adjustments (sitagliptin – caution). Avoid combination drugs that also contain metformin.
- GLP-1 receptor agonists (exenatide, liraglutide): These should not be used in moderate renal function impairment (creatinine clearance <30 mL/min).

Author: Willie Mollentze
Editor: Nazeer A Mohamed

References

1. Rosenberg M, Curhan GC, Sheridan AM. Overview of the management of chronic kidney disease in adults. UpToDate. 2016.
2. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic Kidney Disease: A Report From an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883.
3. Moosa RM, van der Walt I, Naicker S, Meyers AM. Important causes of chronic kidney disease in South Africa. S Afr Med J 2015;105(4):320.
4. Noubiap JJ, Naidoo J, Kengne AP. Diabetic nephropathy in Africa: A systematic review. World J Diabetes. 2015 Jun 10;6(5):759-73. doi: 10.4239/wjd.v6.i5.759.
5. Naicker S. End-stage renal disease in sub-Saharan Africa. Ethn Dis. 2009 Spring;19(1 Suppl 1):S1-13-5.
6. MR Davids, N Marais, JC Jacobs. South African Renal Registry. Annual Report 2012. South African Renal Society, Cape Town 2014.
7. McFarlane P. Gilbert RE, MacCallum L, Senior P. Chronic Kidney Disease in Diabetes. Can J Diabetes 37 (2013) S129eS136.
8. Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, de Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney International, vol. 67 (2005), pp. 2089–2100.
9. Bakris GL, Molitch M. Microalbuminuria as a risk predictor in diabetes: the continuing saga. Diabetes Care. 2014;37(3):867-75.

10. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med 2003;348:2285–2293
11. Zandbergen AA, Baggen MG, Lamberts SW, Bootsma AH, de Zeeuw D, Ouwendijk RJ. Effect of losartan on microalbuminuria in normotensive patients with type 2 diabetes mellitus. A randomized clinical trial. Ann Intern Med. 2003 Jul 15;139(2):90-6.
12. Holtkamp FA, de Zeeuw D, de Graeff PA, Laverman GD, Berl T, Remuzzi G, Packham D, Lewis JB, Parving HH, Lambers Heerspink HJ. Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy: a post hoc analysis of the combined RENAAL and IDNT trials. Eur Heart J. 2011 Jun;32(12):1493-9.
13. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999 Mar 16;130(6):461-70.
14. Mazzucco G, Bertani T, Fortunato M, Bernardi M, Leutner M, Boldorini R, Monga G. Different patterns of renal damage in type 2 diabetes mellitus: a multicentric study on 393 biopsies. Am J Kidney Dis. 2002 Apr;39(4):713-20.
15. Fullerton B, Jeitler K, Seitz M, Horvath K, Berghold A, Siebenhofer A. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2014 Feb 14;2:CD009122.
16. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. Arch Intern Med. 2012 May 28;172(10):761-9.
17. Buehler AM, Cavalcanti AB, Berwanger O, Figueiro M, Laranjeira LN, Zazula AD, Kioshi B, Bugano DG, Santucci E, Sbruzzi G, Guimaraes HP, Carvalho VO,Bordin SA. Effect of tight blood glucose control versus conventional control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized controlled trials. Cardiovasc Ther. 2013 Jun;31(3):147-60.
18. Lv J, Perkovic V, Foote CV, Craig ME, Craig JC, Strippoli GF. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2012 Dec 12;12:CD004136.
19. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. Lancet. 1993 May 22;341(8856):1306-9.
20. Buehler AM, Cavalcanti AB, Berwanger O, Figueiro M, Laranjeira LN, Zazula AD, Kioshi B, Bugano DG, Santucci E, Sbruzzi G, Guimaraes HP, Carvalho VO,Bordin SA. Effect of tight blood glucose control versus conventional control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized controlled trials. Cardiovasc Ther. 2013 Jun;31(3):147-60.
21. Palmer SC, Mavridis D, Navarese E, Craig JC, Tonelli M, Salanti G, Wiebe N, Ruospo M, Wheeler DC, Strippoli GF. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet. 2015 May 23;385(9982):2047-56.
22. Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med. 2004 Nov 4;351(19):1952-61.
23. Anonymous. Effects of Ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE and MICRO-HOPE sub-study. Heart Outcomes Prevention Evaluation Study Investigators. Lancet. 2000 Jan 22;355(9200):253-9.
24. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008 Apr 10;358(15):1547-59.
25. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, Leehey DJ, McCullough PA, O'Connor T, Palevsky PM, Reilly RF, Seliger SL, Warren SR, Watnick S, Peduzzi P, Guarino P; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013 Nov 14;369(20):1892-903.
26. Ren F, Tang L, Cai Y, Yuan X, Huang W, Luo L, Zhou J, Zheng Y. Meta-analysis: the efficacy and safety of combined treatment with ARB and ACEI on diabetic nephropathy. Ren Fail. 2015 May;37(4):548-61.
27. Bakris GL1, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med. 2000 Mar 13;160(5):685-93.
28. Miyamori I, Yasuhara S, Takeda Y, Koshida H, Ikeda M, Nagai K, Okamoto H, Morise T, Takeda R, Aburano T. Effects of converting enzyme inhibition on split renal function in renovascular hypertension. Hypertension. 1986 May;8(5):415-21.
29. Gerstein HC1, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001 Jul 25;286(4):421-6.
30. Gaede P1, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003 Jan 30;348(5):383-93.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 20: Diabetic eye disease

SEMDSA 2017 Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Diabetic eye disease is a leading cause of visual impairment and screening for diabetic retinopathy is indicated in all patients with type 2 diabetes.	A
Aim to optimise glucose, blood pressure and lipid control to reduce the risk and progression of diabetic retinopathy.	A
Screening should begin at diagnosis of type 2 diabetes.	B
Patients without retinopathy or diminished visual acuity should be screened again every 1 to 2 years.	B
Patients should have their visual acuity assessed.	C
The preferred screening method for diabetic retinopathy is either fundal photography or dilated indirect ophthalmoscopy.	C
Urgent referral to an ophthalmologist is indicated if there is sudden severe vision loss; retinal tear and/or detachment; proliferative diabetic retinopathy or severe diabetic macular oedema.	C
Pregnancy may be associated with worsening of retinopathy. Patients should be counselled and screened for diabetic retinopathy prior to pregnancy, or in the first trimester of pregnancy.	B

20.1 Introduction

Diabetic eye disease is a leading cause of visual impairment in the developing world,[1] and is mainly comprised of diabetic retinopathy (DR), which includes diabetic macular oedema (DMO), and cataract formation. It is estimated that a third of people living with diabetes will develop diabetic retinopathy.[2] Diabetic retinopathy is by and large preventable and/or treatable, while cataract surgery can now successfully be performed on a large scale. It is thus imperative that patients are appropriately screened and referred to an ophthalmologist to detect diabetic eye disease. Vision loss is disabling as it results in a loss of independence and an increased risk of falls. In patients with diabetes this is compounded by their difficulty with administering therapies such as insulin as well as self-monitoring of blood glucose levels.

20.2 Prevalence of diabetic eyes disease

It is estimated that approximately 34.6% of people with diabetes or 93 million people worldwide have some form of DR with 10.2% having vision-threatening diabetic retinopathy (VTDR).[2] Screening studies of DR have often detected a high prevalence of cataracts, even in excess of the prevalence of DR[3,4] and thus cataracts remain a common cause of vision loss in patients with diabetes.

20.3 Risk factors for diabetic eye disease

The duration of diabetes is a major risk factor for DR. The prevalence of DR in patients with type 2 diabetes increases two-fold in those with diabetes for up to 19 years compared to those with diabetes for less than 5 years.[5] Proliferative diabetic retinopathy (PDR), the most vision-threatening form of DR develops in 2% of those with diabetes for under 5 years but is present in 25% of those with diabetes for 25 years.[5]

The most important modifiable risk factor is glycaemic control. Poor glucose control is associated with both the development and progression of DR.[6-8] There is evidence that tight glycaemic control will lower these risks and should be the target, if this can be attained safely. Blood pressure and lipid control also decrease the risk of DR.[9] However there is no evidence to support intensive blood pressure control (systolic BP < 120mmHG) to reduce DR.[10] There is evidence that fenofibrate may reduce the progression of DR.[10] Patients who develop diabetic kidney disease are at high risk of also having DR..

20.4 Screening

Patients with significant DR may be asymptomatic and hence screening is important to detect patients in whom intervention may prevent vision loss. Patients and their family members must be educated that they may have significant eye disease that requires treatment even in the absence of symptoms. Since patients with type 2 diabetes may have had many years of undiagnosed diabetes, it is recommended that all such patients should be screened at diagnosis for DR. Ideally this should be done by an ophthalmologist or an optometrist who is trained in detecting DR. This, however, is not always possible in resource limited settings. All screening encounters should begin with a clinical evaluation with emphasis on glycaemic control; duration of diabetes; other co-morbid diseases (hypertension, dyslipidaemia); drug therapy and ocular history.

Although the validity of visual acuity testing to detect DR was previously debated, recent guidelines have suggested that this is of importance in resource restricted settings where the

screening is not done by an ophthalmologist.[11,15,18] Screening should therefore be divided into 2 components: visual acuity and retinal examination.

20.4.1 Visual acuity

Visual acuity can be assessed by trained healthcare providers (HCP) in any of the following ways, depending on resources:

- Refracted visual acuity examination using a 3- or 4-meter visual acuity lane and a high contrast visual acuity chart.[15]
- Presenting visual acuity examination using a near or distance eye chart and a pin-hole option if visual acuity is reduced.[15]
- Presenting visual acuity examination using a 6/12 (20/40) equivalent handheld chart consisting of at least 5 standard letters or symbols and a pin-hole option if visual acuity is reduced.[15]

If visual acuity is less than 6/12 (20/40), the patient requires referral to an ophthalmologist for further evaluation.

20.4.2 Retinal examination

Screening for diabetic retinopathy can be done in the following ways:

- Fundus photographic methods (dilatation improves results):
  - Digital images, 35mm film or Polaroid instant film prints with subsequent grading by trained individuals. The advantage is that it creates a permanent record of the retina. Screening with a mobile fundal camera improved the quality of care for diabetic patients and is feasible in the South African public sector, primary care setting.[12] Retinal photography was found to be effective, acceptable, and cost-effective.[13]
  - The photograph should be evaluated by an ophthalmologist or medical doctor, nurse or optometrist properly certified by an authority such as the Ophthalmological Society of South Africa (OSSA). This method offers the possibility of telemedicine whereby patients can be screened at their primary health centres and the interpretation is done by a trained individual remotely.
- Indirect ophthalmoscopy i.e. dilated slit-lamp ophthalmoscopy[15] (evaluated by ophthalmologists)
- Direct ophthalmoscopy through dilated pupils (evaluated by medical practitioners, optometrists, or ophthalmologists), although this is the least reliable method.

Since few primary healthcare nurses in SA are trained to screen for DR most patients at primary health care level will have to be referred to a skilled professional until fundal photography becomes more widespread. DR should be assessed according to the International Classification of Diabetic Retinopathy and Diabetic Macular Oedema (Table I).[14] If DR is detected the patient should be monitored and referred according to the ICO Guidelines for Diabetic Eye Care (Table II).[15] In addition patients who cannot be evaluated by their primary HCP for DR or VA should also be referred for ophthalmology assessment.

20.4.3 Frequency of screening

In patients without evidence of DR or impaired visual acuity, annual follow-up screening is usually recommended. However in resource limited areas there is evidence that screening every 2 years may be cost-effective in patients with no DR and good glycaemic control.[16]

Table I: International Classification of Diabetic Retinopathy and Diabetic Macular Oedema[14]

Diabetic Retinopathy	**Findings Observable on Dilated Ophthalmoscopy**
No apparent DR	No abnormalities
Mild nonproliferative DR	Microaneurysms only
Moderate nonproliferative DR	Microaneurysms and other signs (e.g., dot and blot haemorrhages, hard exudates, cotton wool spots), but less than severe nonproliferative DR
Severe nonproliferative DR	Moderate nonproliferative DR with any of the following: • Intraretinal haemorrhages (≥20 in each quadrant); • Definite venous beading (in 2 quadrants); • Intraretinal microvascular abnormalities (in 1 quadrant); • and no signs of proliferative retinopathy
Proliferative DR	Severe nonproliferative DR and 1 or more of the following: • Neovascularization • Vitreous/preretinal haemorrhage
Diabetic Macular Oedema	**Findings Observable on Dilated Ophthalmoscopy#**
No DMO	No retinal thickening or hard exudates in the macula
Noncentral-involved DMO	Retinal thickening in the macula that does not involve the central subfield zone that is 1mm in diameter
Central-involved DMO	Retinal thickening in the macula that does involve the central subfield zone that is 1mm in diameter

Hard exudates are a sign of current or previous macular edema. DMO is defined as retinal thickening, and this requires a three-dimensional assessment that is best performed by a dilated examination using slit-lamp biomicroscopy and/or stereo fundus photography.

Table II: Re-examination and Referral Recommendations based on International Classification of Diabetic Retinopathy and Diabetic Macular Oedema (adapted from ICO Guidelines for Diabetic Eye Care)[15]

Diabetic Retinopathy (DR)		
Classification	**Re-examination Or next screening schedule**	**Referral to Ophthalmologist**
No apparent DR, mild nonproliferative DR and no DMO	Re-examination in 1-2 year	Referral not required
Mild nonproliferative DR	6-12 months	Referral not required
Moderate nonproliferative DR	3-6 months	Referral required
Severe nonproliferative DR	< 3-months	Referral required
PDR	< 1 month	Referral required
Diabetic Macular Oedema (DMO)		
Classification	Re-examination Or next screening schedule	Referral to Ophthalmologist
Noncentral-involved DMO	3 months	Referral required
Central-involved DMO	1 month	Referral required

20.5 Referral to ophthalmology

Patients with DR and other eye diseases usually require referral to ophthalmologists. Table III is a guide is a guide to the urgency of this referral.

20.6 Management of patient with diabetic eye disease

The detailed ophthalmological management of patients with diabetic eye disease is beyond the scope of this guideline. Photocoagulation surgery and anti-vascular endothelial growth factor therapy are the modalities used by ophthalmologists to treat patients with DR and DMO.

The role of the primary HCP is to ensure optimal glycaemic, blood pressure and lipid control to limit progression of DR. It must be borne in mind that rapid intensification of glycaemic control may result in acute worsening of DR;[17] therefore these patients may benefit from treatment for significant DR prior to intensification. Good glycaemic control should not be delayed unnecessarily as the benefits outweigh the risks. In addition, patients with DR are likely to have other microvascular complications and patients should be screened for diabetic kidney disease and neuropathy. Patients who are visually disabled should be assisted with appropriate disability grants and rehabilitation.

20.7 Pregnancy

Pregnancy may be associated with progression of DR.[19,20] Women with pre-existing type 2 diabetes who are planning pregnancy or who have become pregnant should be counselled on the risk of development and progression of DR. These women often have rapid intensification of glycaemic control which may further compound this risk.[17] They should be screened prior to falling pregnant or within the first trimester for DR. On the other hand, women with gestational diabetes are not at increased risk and do not require screening for DR.[21]

Authors: Nazeer A Mohamed and Willie Mollentze

Table III: Referral to ophthalmology[18]

Urgent referral:
- Sudden severe vision loss
- Retinal tear and/or detachment
- Proliferative diabetic retinopathy
- Severe DMO

Referral within three months:
- Unexplained gradual worsening of vision
- Non central-involved DMO
- Visual acuity below 6/12 (20/40)
- Severe nonproliferative diabetic retinopathy
- Symptomatic vision complaints

Referral within six months:
- Unexplained retinal findings
- Visual acuity cannot be obtained
- Retinal examination cannot be obtained or inability to visualise fundus
- Glaucoma
- Cataract
- Moderate nonproliferative diabetic retinopathy (no DMO)
- Mild nonproliferative diabetic retinopathy

References

1. Klein BE. Overview of epidemiologic studies of diabetic retinopathy. Ophthalmic Epidemiol 2007;14:179-83
2. Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012 Mar;35(3):556–64.
3. Khan T, Bertram MY, Jina R, Mash B, Levitt N, Hofman K. Preventing diabetes blindness: Cost effectiveness of a screening programme using digital non-mydriatic fundus photography for diabetic retinopathy in a primary health care setting in South Africa. Diabetes Res Clin Pract. 2013 Aug;101(2):170-6
4. Bai XL, Xu X, Lu M, et al. A cross-sectional study of moderate or severe visual impairment and blindness in residents with type 2 diabetes living in Xinjing Town, Shanghai. Chin J Ophthal.2016 Nov; 52: 825-830
5. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 1984;102:527-32.
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
7. Kohner EM, Stratton IM, Aldington SJ, et al. Relationship between the severity of retinopathy and progression to photocoagulation in patients with Type 2 diabetes mellitus in the UKPDS (UKPDS 52). Diabet Med 2001;18:178-84.

8. Wong TY, Liew G, Tapp RJ, et al. Relation between fasting glucose and retinopathy for diagnosis of diabetes: three population-based cross-sectional studies. Lancet 2008;371:736-43.
9. Leske MC, Wu S-Y, Hennis A, et al. Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. Ophthalmology 2005;112:799–805
10. ACCORD Study Group, ACCORD Eye Study Group, Chew EY, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes.N Engl J Med 2010;363:233–244
11. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy: ETDRS report number 9. Ophthalmology 1991;98:766-85. (Vis acuity)
12. Mash B, Powell D, du Plessis F, et al. Screening for diabetic retinopathy in primary care with a mobile fundal camera – evaluation of a South African pilot Project. S Afr Med J 2007; 97: 1284-1288
13. O'Hare JP, Hopper A, Madhaven C, et al. Adding retinal photography to screening for diabetic retinopathy: a prospective study in primary care. BMJ. 1996 Mar 16;312(7032):679-82
14. Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1679.
15. Wong TY, Aiello LP, Ferris F, et al. ICO Guidelines for Diabetic Eye Care http://www.icoph.org/downloads/ICOGuidelinesforDiabeticEyeCare.pdf
16. Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. Diabetes Care 011;34:1318– 1319
17. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998; 116:874-86
18. International Diabetes Federation and The Fred Hollows Foundation. Diabetes eye health: A guide for health care professionals. Brussels, Belgium: International Diabetes Federation, 2015. www.idf.org/eyecare
19. Axer-Siegel R, Hod M, Fink-Cohen S, et al.Diabetic retinopathy during pregnancy. Ophthalmology 1996;103:1815–1819
20. Best RM, ChakravarthyU. Diabetic retinopathy in pregnancy. Br J Ophthalmol 1997;81:249–251
21. Gunderson EP, Lewis CE, Tsai A-L, et al. A 20-year prospective study of childbearing and incidence of diabetes in young women, controlling for glycemia before conception: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Diabetes 2007;56:2990–2996

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 21: The prevention and treatment of foot problems in diabetes

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
This section should be read in conjunction with Appendices 21.1 to 21.5	
In people with diabetes, foot examinations by healthcare providers must be an integral component of diabetes management to identify persons at risk for ulceration and lower-extremity amputation.	B
All patients with type 2 diabetes must have their bare feet examined at least annually (more frequently in those with a high risk for ulcers) in an attempt to prevent foot ulceration.	C
The foot assessment must include a formal assessment for skin, bone and joint, nerve and vascular abnormalities (as outlined in Appendix 21.2).	C
Screening for peripheral neuropathy should be conducted by assessing loss of sensitivity to the 10g monofilament or loss of sensitivity to vibration at the dorsum of the great toe.	B
All patients with type 2 diabetes should receive education on good footcare practices and ulcer prevention.	C
People at **high risk** of foot ulceration and amputation should receive more frequent and intensive foot care **education**, and be referred to healthcare professionals trained in footcare management.	B
Patients with a plantar foot ulcer, critical limb ischaemia, gangrene or Charcot foot must be referred urgently for specialist care to a centre with multidisciplinary care.	C
People with diabetes should be treated, whenever possible, with intensified glycaemic control to prevent the onset and progression of neuropathy, for type 1 diabetes and for type 2 diabetes.	A
The following agents may be used alone or in combination for relief of painful peripheral neuropathy: ◦ tricyclic antidepressants (amitriptyline) ◦ serotonin–noradrenaline reuptake inhibitors (duloxetine, venlafaxine) ◦ anticonvulsants (pregabalin, and gabapentin).	A

21.1. Introduction

This chapter highlights the morbidity and mortality associated with distal peripheral sensory diabetic neuropathy and other foot problems leading to ulceration and amputation. Ulceration and amputation are preventable complications of diabetes and the health care provider should execute the necessary measures as outlined in this guideline in order to ensure optimal patient outcomes. *The annual foot assessment in the asymptomatic patient is an obligatory component of good diabetes care.*

This guideline is an update of the 2012 SEMDSA guideline, and expands the practical aspects of foot-care, as well as referral strategies.

21.1.1 Defining the problem

The term "diabetic foot" is a generic one referring to a variety of pathological conditions that can affect the foot in patients with diabetes. Foot problems are a major cause of morbidity and mortality in people with diabetes, and contribute to increased healthcare costs.[1-3] The sequence of events leading to lower-extremity amputation is well known. In people with neuropathy and/or peripheral artery disease (PAD), minor trauma to the foot leads to skin ulceration, infection and ultimately gangrene, resulting in amputation.[4-10] The lifetime risk for foot ulceration in diabetes patients ranges from 10 to 25%,[11] and foot complications are the major reason for admission to hospital for people with diabetes, accounting for approximately 20%-30% of all diabetes-related admissions in the North American population.[8,9,12-14] Unfortunately no such data exists for the South African population. Ethnic differences noted in western countries suggest that South Asians from the Indian subcontinent have lower rates of foot ulcers and amputations, while African-Americans have higher rates than white Caucasians.

All patients with type 2 diabetes should have an annual foot assessment to determine their ulcer risk.[11] A random survey of 18 community health centres in the Western Cape in 2008 found that only 11.3% of patients with diabetes had a recorded foot examination.[15] Similarly, a study of 750 diabetes records at a regional hospital in Kwa Zulu Natal revealed that a foot examination was recorded in only 6% of patients.[16] It is well known that after amputation of one limb, the prognosis for the contralateral limb is poor.[17,18] What is not often appreciated though, is that the 5-year mortality following a diabetic foot

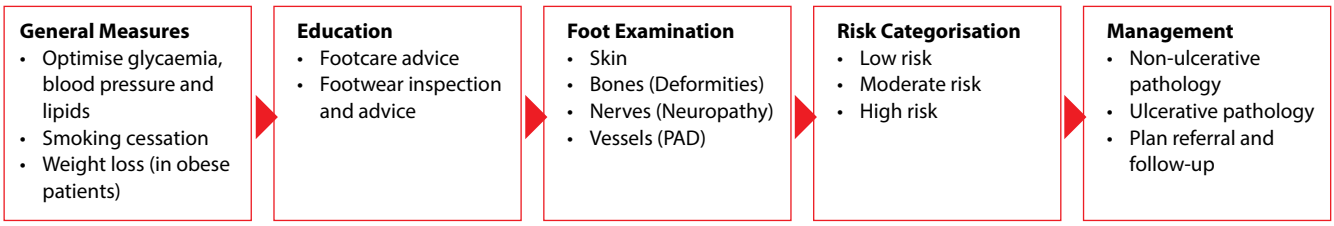


Figure I: The diabetic foot ulcer prevention plan

ulcer or an amputation is 50% and 70% respectively, and exceeds that of many malignancies.[19] Preventing the first ulcer and amputation is therefore of paramount importance.

21.1.2 Identifying risk factors for ulceration[1,20,21]

Characteristics that have been shown to confer high risk of ulceration include:

- Previous ulceration
- Neuropathy
- Structural foot deformity and limited joint mobility
- Peripheral arterial disease (PAD)
- Microvascular complications (i.e. retinopathy, nephropathy). Patients on renal replacement therapy (e.g. dialysis) are at particularly high risk.[11] Any foot assessment must therefore, of necessity, include an evaluation for these risk factors.

21.1.3 Understanding the pathogenesis of foot ulcer development[22]

A crucial component of the pathogenesis of foot ulceration is most often *chronic distal sensorimotor neuropathy*.[23] This is present, to some degree, in more than 50% of people with diabetes who are older than 60 years.[24] Peripheral neuropathy must usually be profound before leading to *loss of the protective sensation (LOPS)* in the absence of which patients become vulnerable to trauma; the consequent vulnerability to physical and thermal trauma increases the risk of foot ulceration sevenfold.[25,26]

A second causative factor in foot ulceration is *excessive plantar pressure*.[27] This is related to both limited joint mobility (at the ankle, subtalar and first metatarsophalangeal joints) and foot deformities.[28-30] Excessive plantar pressure is recognised when seeing callus on the plantar surface of the foot, typically over the metatarsal heads. In one study of patients with peripheral neuropathy, 28% with high plantar pressure developed a foot ulcer during a 2.5-year follow-up, compared with none with normal pressure.[31]

A third component is *trauma*, particularly when repetitive. Among 669 people observed with foot ulcers, 21% were attributed to rubbing from footwear, 11%were linked to injuries (mostly falls), 4% to cellulitis complicating tinea pedis, and 4% to self-inflicted trauma (e.g. cutting toenails).[32] Those who had had a previous foot ulceration could withstand fewer cycles of stress to their feet before an ulcer recurred.[33]

Peripheral arterial disease (PAD) with obstruction of the arteries to the lower legs and feet also increases the risk of ulceration, and is a crucial factor in the delayed healing of foot ulcers. People with PAD may present with symptoms of ischaemia, such as claudication, rest pain, ulceration or gangrene. However, it is important to remember that people with diabetes often present without any history of these typical symptoms of ischaemia, because most of have established peripheral neuropathy as well. PAD in people with diabetes also occurs at an earlier age and progresses more rapidly.[34,35]

21.2. Prevention of foot ulceration and amputation

The prevention and management of foot complications can be divided into a convenient 5 step approach (Figure I).

A foot examination should form part of the annual review of patients with diabetes in order to detect risk factors for ulceration. This is usually performed by a healthcare professional (HCP) proficient in the assessment of feet, but community health care workers can also be trained to do this in resource poor communities.

21.2.1 General prevention strategies

These include optimising treatment of elevated blood glucose, blood pressure (BP) and cholesterol, as well as advice on smoking cessation. This is essential to prevent microvascular and macrovascular complications of diabetes. Weight loss in obese individuals is important to reduce abnormal pressure on the foot.

21.2.2 Education about foot-care and footwear (Appendix 21.1)

The patient and his/her caregiver should be advised by the healthcare professional on appropriate foot care. Effective foot care involves a partnership between patients, their caregivers and health professionals, and all parties should agree upon all decisions. Extra vigilance and a routine foot care programme should be employed in the older person with poor vision and mobility, who is possibly socially deprived and lives alone. Different patient education approaches should be applied to promote improved foot care. Structured education programmes should be considered at the time of diagnosis, and should be recommended to the patients as required on an ongoing basis.

Appendix 21.1 outlines some of the aspects that should be covered when educating patients and caregivers about self-care and the choice of footwear. This is conveniently divided into a checklist of things that they should and should not do.

In addition, the healthcare provider should inspect the patient's footwear at every visit. The patient should wear good shoes that fit well, and the health care provider should check that the shoes:

- Are the correct length and width.
- Allow enough room for the toes (high toe box).
- Have a smooth inner lining without seams.
- Have a flexible sole that can bend easily and is non-slip.
- Have a heel no higher than 4 cm.

The use of a foot template to select the length and width of shoes should be encouraged especially in patients with diminished sensation (Appendix 21.1, Figure II). The patient must stand (the foot widens substantially with weight bearing) on a piece of cardboard while someone traces the outline of the weight bearing foot. This template should fit into the selected shoe without the edges folding.

Patients with sensory loss or a history of foot ulceration should receive intensive and repetitive education on the correct fit of shoes and early signs of ill-fitting shoes. These patients should also be referred to a podiatrist or orthotist for in-shoe pressure analysis and for therapeutic shoes to prevent plantar foot ulceration or reulceration.[36]

21.2.3 Regular examination of the feet (Appendix 21.2)

The comprehensive foot examination must be performed at diagnosis of type 2 diabetes, and if normal, repeated annually thereafter.[37] It is worth noting that in the UKPDS study, 13% of patients had neuropathy of sufficient severity to put them at risk for foot ulceration at the time of diabetes diagnosis.[11] An abnormal foot examination will warrant more frequent foot examinations (see "Risk categorisation" below).

The foot examination includes an assessment of the skin, bones, nerves and vasculature of the feet by a trained health care professional (Appendix 21.2).

21.2.3.1 Skin Assessment (Appendix 21.3)

It is important to look for ulcers, scars from previous ulcers, corns, calluses, fissures, fungal infections (particularly between the toes), blisters and signs of trauma. Areas of redness, and imprints of the socks or shoes on the skin may indicate ill-fitting stockings and footwear. Callus on the plantar surface over the metatarsal heads is important, as this indicates high plantar pressure. A dusky discolouration of the foot and diminished hair growth on the lower leg may indicate peripheral arterial disease (PAD).

The foot examination should also include a skin temperature assessment (with back of hand). Increased warmth is the first indicator of inflammation in an insensate foot. It may also indicate acute Charcot neuroarthropathy, a complication of the loss of protective sensation in the foot.[38-40] This results in bony changes, and/or fractures, subluxations and dislocations. In addition, an acute Charcot neuroarthropathy foot may be associated with erythema and swelling, with overall clinical characteristics very similar to cellulitis. It may also need to be distinguished from osteomyelitis (especially if a foot ulcer is present).[41,42]

Some skin abnormalities are illustrated in Appendix 21.3.

21.2.3.2 Bone (Deformity) Assessment (Appendix 21.3)

Foot deformities increase the risk of ulceration. The presence of any of the following must be documented:

- Bunion (hallux valgus)
- Hammer toes
- Arch abnormalities e.g. pes cavus, pes planus
- Limited joint mobility at the ankle or big toe
- Other bony prominences or deformities
- Features of acute or chronic Charcot neuroarthropathy.

Refer to Appendix 3 for illustrations.

21.2.3.3 Nerves (Neuropathy Assessment) (Appendix 21.4)

The examiner should test for the loss of protective sensation. Ideally, this should be done using a 10 g Semmes Weinstein monofilament *or* a 128 Hz tuning fork. The monofilament test is the preferred test.[43] Note that the monofilament test as described is aimed at *detecting neuropathy*, not at identifying sites at risk of ulceration. If neuropathy is detected, plantar sites should be tested (plantar surfaces of first, third and fifth metatarsal and distal plantar surface of first toe as examples). A neurothesiometer can be used in a specialised setting.

Note that the aim of clinical examination is to determine the foot at risk. Unfortunately the monofilament test has not been standardised and testing varies from 1 to 10 sites. The Canadian Guideline uses a single test on the dorsum of the big toe.[44] A monofilament test with 7 or 8 correct responses (out of 8) effectively rules out neuropathy. So any score less than this means the patient must be regarded as "At Risk" as neuropathy cannot be excluded and the patient should be managed as "At Risk". (If one wants to be certain that there is neuropathy, one needs 5 or more incorrect responses.) The same is true for the test with the tuning fork.[45]

Our guideline retains agreement with the 2008 Canadian Guideline[1] in identifying the possible presence of neuropathy with the tuning fork or monofilament. The 2013 Canadian Guideline uses the same test but with a scoring system to indicate who would possibly develop neuropathy over the next four years.[46] SEMDSA has not adopted this recommendation because complicated scoring systems are not easy to recall in primary care, and the tuning fork test could not predict incident neuropathy over four years.

If a monofilament or tuning fork is not available, a cotton wool ball or the fingertips can be used to test sensation by lightly touching the plantar surfaces of the feet, under the first, third and fifth toes. This is the Ipswich Touch the Toes test (refer to 21.4 for details) and it has been validated against the monofilament. Neuropathy is defined as two or more insensitive sites out of these six.[47]

21.2.3.4 Vasculature

The dorsalis pedis (on the top of the foot) and tibialis posterior pulses (behind the medial malleolus) should be palpated. If both are absent, the likelihood for PAD increases.

The patient should be asked about pain in the calves when walking. PAD is more likely if intermittent claudication is present and both pulses are absent in the same limb. However, the atypical presentation of "ischaemia without symptoms" can manifest in patients with diabetes.

Table I. Risk categorisation system for diabetic feet.[Adapted from 43 and 48]

Category	Risk profile	Frequency of foot examinations / level of care
Low risk	People with no risk factors and no previous history of foot ulcer/ amputation	General footcare and education; annual examination at primary care
Moderate risk	People with one risk factor (neuropathy, peripheral arterial disease or foot deformity) *and* no previous history of foot ulcer/amputation	Every visit Secondary level care
High risk	People with two or more risk factors (neuropathy, peripheral arterial disease or foot deformity) and/or a previous history of foot ulcer/ amputation[1]	Every visit Tertiary level care
Active foot problem	People with ulceration or spreading infection or critical limb ischaemia or gangrene or suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain.	Every visit

21.2.4 Risk stratification and follow-up

After examination of the feet, the patient's risk stratification should be determined, and he or she should be evaluated accordingly (Table I). Appendix 21. 5 illustrates the comprehensive pathway of care for the different risk categories.

Patients identified as being at intermediate or high risk (category 1 and 2) for ulceration must receive intensive education focussing on prevention, and also routine treatment of non-ulcerative foot pathology by a podiatrist if possible or alternatively by a trained health care worker.

21.3. Specific management of positive findings on the foot examination

21.3.1 Painless neuropathy with loss of protective sensation

Note that not all patients have painful neuropathy. When there is loss of protective sensation (painless or painful neuropathy) the patient is regarded as being at risk for ulceration. Patient education, referral as needed (see below) and frequent examination (see Table I) are crucial in order to avoid foot ulceration.

21.3.2 Painful peripheral neuropathy

A recent meta-analysis recommends tricyclic antidepressants, serotonin–noradrenaline reuptake inhibitors, pregabalin, and gabapentin as first-line neuropathic pain therapy.[49]

If the patient still has severe symptoms, in spite of a trial of a minimum of 14 days of any of the above, he or she should be referred to the secondary-care level.

Patients with suspected Charcot foot must be referred to a hospital where orthopaedic surgical and podiatrist services are available.

21.3.3 Non-ulcerative foot pathology

Pathology requiring podiatric or orthopaedic care.

Depending on the available referral network, all patients with severe non-ulcerative foot pathology (e.g. corns, calluses, nail deformities or hypertrophy, foot deformities) should be seen by a podiatrist and an orthotist. Severe foot deformities could be referred to an orthopaedic surgeon.

21.3.4 Suspected peripheral arterial disease.

If both pedal pulses are absent in either foot, with or without symptoms of chronic ischemia, the patient should be referred to a centre where vascular surgery is available. Symptoms of ischaemia include intermittent claudication and/or rest pain. Signs of ischaemia include skin thinning, loss of hair growth, nail thickening, pallor on elevation, dependent rubor, ulceration and distal gangrene. If a patient has a foot ulcer with ANY absent foot pulse (dorsalis pedis OR tibialis posterior) they should have a full vascular assessment (Doppler studies).

In the interim, the cardiovascular risk management should be optimised as per the SEMDSA guideline.

21.3.5 Ulcerative foot pathology

These patients should if at all possible be referred to a diabetes clinic or foot clinic at secondary or tertiary care level.

Please refer to Wound Healing Association of South Africa (WHASA) consensus document of the management of the diabetic foot ulcer[50] and the International Working Group on the Diabetic Foot (IWGDF) guidance on the diagnosis and management of foot infections in persons with diabetes.[51]

Authors: Paul Rheeder, Gerda Van Rensburgh, Naomi S Levitt and Aslam Amod
Editors: Joel A Dave

References

1. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes. 2008;32(suppl 1): S143-S146.
2. American Diabetes Association: clinical practice recommendations 2004. Diabetes Care. 2004;27(Suppl 1):S63-S64.
3. Reiber GE, Boyko EJ, Smith DG. Lower extremity foot ulcers and amputations in diabetes. In: Diabetes in America. 2nd ed. Bethesda: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995; NIH Publication No. 95-1468 p. 409-428.
4. Eastman RC. Neuropathy in diabetes. In: Diabetes in America. 2nd ed. Bethesda: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995; NIH Publication No. 95-1468,p. 339-348.
5. Palumbo PJ, Melton LJ III. Peripheral vascular disease and diabetes. In: Diabetes in America. 2nd ed. Bethesda: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995; p. 401-408.
6. Boyko EJ, Lipsky BA. Infection and diabetes. In: Diabetes in America. 2nd ed. Bethesda: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995; p. 485-499.

7. Frykberg RG. Diabetic foot ulcerations. In: Frykberg RG, ed. The high risk foot in diabetes mellitus. New York: ChurchillLivingstone, 1991; p. 151-195.
8. Frykberg RG, Veves A. Diabetic foot infections. Diabetes Metab Rev. 1996;12:255-270.
9. Gibbons GW, Eliopoulos GM, Kozak GP, et al. Infection of the diabetic foot. In: Kozak GP, Campbell DR, Frykberg RG, et al, eds. Management of diabetic foot problems. Philadelphia: W B Saunders, 1995; p. 121.
10. Reiber GE, Pecoraro RE, Koepsell TD. Risk factors for amputation in patients with diabetes mellitus. A case-control study. Ann Intern Med. 1992;117:97-105.
11. Boulton AJM. The Diabetic Foot. [Updated 2016 Oct 26]. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK409609/
12. Bild DE, Selby JV, Sinnock P, et al. Lower-extremity amputation in people with diabetes. Epidemiology and prevention. Diabetes Care. 1989;12:24-31.
13. Reiber GE. Epidemiology of the diabetic foot. In: Levin ME, O'Neal LW, Bowker JH, eds. The diabetic foot. 5th ed. St Louis: Mosby, 1993; p. 1-15.
14. Department of Health and Human Services, Centers for Disease Control and Prevention. Number (in Thousands) of Hospital Discharges with a Lower Extremity Condition (LEC) as First-Listed or Secondary Diagnosis and Diabetes as Any Listed Diagnosis, United States, 1988–2007 [cited 1 April 2016]. Available from: http://www.cdc.gov/diabetes/statistics/hosplea/diabetes_complications/fig5.htm
15. Steyn K, Levitt NS, Patel M, Gwebushe N, Lombard C, Everett K. Hypertension and diabetes: Poor care for patients at community health centres. J Endocrinol Metab Diabetes South Africa. 2008;13(2):64-70. doi:10.1080/22201009.2008.10872172.
16. Igbojiaku OJ, Harbor OC, Ross A. Compliance with diabetes guidelines at a regional hospital in KwaZulu-Natal, South Africa. African J Prim Heal Care Fam Med. 2013;5(1):1-5. doi:10.4102/phcfm.v5i1.447.
17. Ebskov B, Josephsen P. Incidence of reamputation and death after gangrene of the lower extremity. Prosthet Orthot Int. 1980;4:77-80.
18. Most RS, Sinnock P. The epidemiology of lower extremity amputations in diabetic individuals. Diabetes Care. 1983;6:87-91.
19. Armstrong, D. G., Wrobel, J. and Robbins, J. M. (2007), Guest Editorial: are diabetes-related wounds and amputations worse than cancer?. International Wound Journal, 4: 286–287. doi:10.1111/j.1742-481X.2007.00392.x
20. Boyko EJ, Ahroni JH, Stensel V, et al. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. Diabetes Care. 1999;22:1036-1042.
21. Fernando DJ, Masson EA, Veves A, et al. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. Diabetes Care. 1991;14:8-11.
22. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293:217-2
23. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. Diabetes Care. 1990;13:513-521.
24. Young MJ, Boulton AJ, MacLeod AF, et al. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993;36:150-154.
25. Reiber GE, Vileikyte L, Boyko EJ, et al. Causal path-ways for incident lower-extremity ulcers in patients with diabetes from two settings. Diabetes Care. 1999;22:157-162.
26. Young MJ, Breddy JL, Veves A, Boulton AJ. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds: a prospective study. Diabetes Care. 1994;17:557-560.
27. Sanders LJ. Diabetes mellitus: prevention of amputation. J Am Podiatr Med Assoc. 1994;84:322-328.
28. Zimny S, Schatz H, Pfohl M. The role of limited joint mobility in diabetic patients with an at-risk foot. Diabetes Care. 2004;27:942-946.
29. Fernando DJ, Masson EA, Veves A, Boulton AJ. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. Diabetes Care.1991;14:8-11.
30. Mueller MJ, Hastings M, Commean PK, et al. Forefoot structural predictors of plantar pressures during walking in people with diabetes and peripheral neuropathy. J Biomech. 2003;36:1009-1017.
31. Veves A, Murray HJ, Young MJ, Boulton AJ. The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study. Diabetologia. 1992;35:660-663.
32. Macfarlane RM, Jeffcoate WJ. Factors contributing to the presentation of diabetic foot ulcers. Diabet Med. 1997;14:867-870.
33. Maluf KS, Mueller MJ. Novel Award 2002: Comparison of physical activity and cumulative plantar tissue stress among subjects with and without diabetes mellitus and a history of recurrent plantar ulcers. Clin Biomech (Bristol, Avon). 2003;18:567-575.
34. Jude EB. Intermittent claudication in the patient with diabetes. Br J Diabetes Vasc Dis. 2004;4:238-242.
35. Jude EB, Ojibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care. 2001;24:1433-1437.
36. Sicco A. Bus S.A,R Haspels R,Busch-Westbroek T.E. Evaluation and Optimization of Therapeutic Footwear for Neuropathic Diabetic Foot Patients Using In-Shoe Plantar Pressure Analysis . Diabetes Care. 2011: 34:1595-1600.
37. Boulton AJ, Armstrong DG, Albert SF, et al, American Diabetes Association, American Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care 2008;31:1679e85.
38. Lavery LA, Higgins KR, Lanctot DR, et al. Preventing diabetic foot ulcer recurrence in high-risk patients: use of temperature monitoring as a self-assessment tool. Diabetes Care. 2007;30:14-20.
39. Armstrong DG, Lavery LA. Monitoring healing of acute Charcot's arthropathy with infrared dermal thermometry. J Rehabil Res Dev. 1997;34:317-321.
40. Yu GV, Hudson JR. Evaluation and treatment of stage 0 Charcot's neuroarthropathy of the foot and ankle. J Am Podiatr Med Assoc. 2002;92:210-220.
41. Frykberg RG, Zgonis T, Armstrong DG, et al; American College of Foot and Ankle Surgeons. Diabetic foot disorders. A clinical practical guideline (2006 revision). J Foot Ankle Surg. 2006;45(5 suppl):S1-S66.
42. Ledermann HP, Morrison WB. Differential diagnosis of pedalosteomyelitis and diabetic neuroarthropathy: MR imaging. Semin Musculoskelet Radiol. 2005;9:272-283.
43. National Institute for Health and Care Excellence (NICE). Diabetic foot problems: prevention and management. NICE guideline [NG19] Published date: August 2015 Last updated: January 2016 https://www.nice.org.uk/guidance/ng19 [Accessed 30 July 2016]
44. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Bril V, Perkins B, Toth C. Neuropathy. Can J Diabetes. 2013 Apr;37 Suppl 1:S142-4. doi: 10.1016/j.jcjd.2013.01.039.
45. Perkins BA, Olaleye D, Zinman B, et al. Simple screening tests for peripheral neuropathy in the diabetes clinic. Diabetes Care. 2001;24:250-256.
46. Perkins BA, Orszag A, Ngo M, Ng E, New P, Bril V. Prediction of incident diabetic neuropathy using the monofilament examination: a 4- year prospective study. Diabetes Care. 2010;33:1549-54.
47. Rayman G, Vas PR, Baker N, et al. The Ipswich touch test: a simple and novel method to identify inpatients with diabetes at risk of foot ulceration. Diabetes Care. 2011;34(7):1517-1518.
48. Avaialble from https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/diabetes_foot_full_guideline_23062011.pdf (cited on 22 Feb 2016)
49. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. Lancet Neurol 2015 Feb; 14:162-173.
50. Available from http://www.woundhealingsa.co.za/index.php/WHSA/article/view/185, (cited on 24 February 2016)
51. Lipsky BA, Aragón-Sánchez J, Diggle M, Embil J, Kono S, Lavery L, Senneville É, Urbančič-Rovan V, Van Asten S; International Working Group on the Diabetic Foot (IWGDF). IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab Res Rev. 2016 Jan;32 Suppl 1:45-74.
52. Crawford F, Inkster M, Kleijnen J, Fahey T. Predicting foot ulcers in patients with diabetes: a systematic review and meta-analysis. QJM 2007;100:65e86.
53. Feng Y, Schlösser FJ, Bauer E, Sumpio BE. The Semmes Weinstein monofilament examination is a significant predictor of the risk of foot ulceration and amputation in patients with diabetes mellitus. J Vasc Surg 2011;53:220e6.
54. Arad Y, Fonseca V, Peters A, Vinik A. Beyond the monofilament for the insensate diabetic foot. Diabetes Care 2011;34:1041e6.
55. Valk GD, Kriegsman DM, Assendelft WJ. Patient education for preventing diabetic foot ulceration: a Systematic review. Endocrinol Metab Clin North Am 2002;31:633e58.
56. McCabe CJ, Stevenson RC, Dolan AM. Evaluation of a diabetic foot screening and protection programme. Diabet Med 1998;15:80e4.
57. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Bowering K, Embil JM. Foot Care. Can J Diabetes. 2013;37 Suppl 1:S145-9.
58. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of longterm complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977e86.
59. Reichard P, Berglund B, Britz A, et al. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm Diabetes Intervention Study (SDIS) after 5 years. J Intern Med 1991;230:101e8.
60. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352: 837e53.
61. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Bril V, Perkins B, Toth C. Neuropathy. Can J Diabetes. 2013;37 Suppl 1:S142-4.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Chapter 22: Diabetes care in pregnancy

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations.

Classification and Diagnosis

- The WHO classification of hyperglycaemia first detected in pregnancy has changed, and now includes "gestational diabetes" and "diabetes mellitus in pregnancy/overt diabetes".
- The diagnostic criteria for gestational diabetes has changed. We currently adopt the IADPSG criteria.

Screening

- Pregnant women considered at high-risk for diabetes should be offered a 75 g 2-hour OGTT at their first visit (Grade B) and a further test at 24-28 weeks if the first test is normal (Grade A).

Referral

- Diabetes in pregnancy is a high-risk condition and must be referred to specialist diabetes centres for management (Grade C).

Preconception

- Preconception counseling should occur (Grade A), and an HbA_{1c} <6.5% (Grade B) should be achieved for at least three months just prior to conception to minimize the incidence of congenital anomalies.
- Folate (5 mg/day) should be taken from three months preconception to 12 weeks of gestation (Grade A).
- Hypertensive patients should achieve an acceptable BP of <130/80 mm Hg and discontinue ACE inhibitors and ARB therapies (Grade A).
- Statin therapy should be discontinued (Grade A).

Pharmacological management of diabetes during pregnancy

- Insulin is the preferred therapy for diabetes in pregnancy. Both human (Grade A) and some analogue insulins (Grade B) may be given during pregnancy as multiple daily injections, striving for normoglycaemia.
- Non-insulin oral agents: both metformin and glibenclamide may be prescribed/continued during pregnancy under specialist supervision (Grade B).

Timing of delivery

- For pre-existing type 1 and type 2 diabetes, and diabetes in pregnancy/overt diabetes
  - Uncomplicated pregnancy- aim for elective delivery between 37-38 weeks gestation (Grade B).
  - Complicated pregnancy- aim for delivery prior to 37 weeks gestation (Grade B).
- Gestational diabetes and
  - Uncomplicated pregnancy- safe to continue pregnancy to 39-40 weeks gestation (Grade B).
  - Complicated pregnancy- delivery prior to 40 weeks is advocated (Grade C).

Postpartum care

- All neonates born to mothers with diabetes should be delivered in a tertiary care centre and be assessed by a neonatologist (Grade A).
- All patients with hyperglycaemia in pregnancy and normoglycaemia post-delivery should be reassessed with a 2-hour OGTT at 6 weeks postpartum (Grade A). Annual screening for diabetes should be performed if the result is normal (Grade B).
- Patients with pre-existing type 1 or type 2 diabetes may resume their pre-conception oral and/or insulin therapy.
- Patients with overt/gestational diabetes with persistent hyperglycaemia immediately postpartum should be managed accordingly.

Caution should be advised regarding hypoglycaemia if breastfeeding.

22.1 Introduction

There has been a major revision since the 2012 guideline to the classification and diagnosis of hyperglycaemia which is detected for the first time in pregnancy.

Great strides have been made in the management of diabetes mellitus in pregnancy in recent years. As a result of the epidemic of obesity, more young women are being diagnosed with gestational diabetes and overt diabetes in pregnancy. This section serves to classify the different types of diabetes in pregnancy, the current and proposed criteria for diagnosis, and the principles of management. A diabetes-obstetrics healthcare team should, ideally, be responsible for the comprehensive management of these women. Excellent care throughout (and, in certain cases, prior to) pregnancy ensures a successful outcome in the vast majority of these pregnancies.

22.2 Prevalence

The prevalence of diabetes mellitus (diabetes) in pregnancy has been increasing worldwide, with the vast majority being due to gestational diabetes and the remainder due to disease predating the pregnancy i.e. pregestational diabetes. A global prevalence estimate of hyperglycaemia in pregnancy is 16.9%.[1,2] To date, there remains a paucity of data regarding the prevalence of gestational diabetes in Africa.[3]

22.3 Risks associated with uncontrolled diabetes in pregnancy

Uncontrolled diabetes during pregnancy poses numerous risks for the mother and foetus /neonate (Table I). In addition, diabetes in pregnancy increases the risk of obesity and Type 2 diabetes in the offspring later in life.[4]

Table I. Maternal, foetal/neonatal complications

Maternal	Foetal	Neonatal
Pre-eclampsia	Miscarriage	Respiratory distress syndrome
Polyhydramnios	Stillbirth	Hypoglycaemia
Pre-term delivery	Macrosomia	Hyperbilirubinemia
Acceleration of vascular disease	Congenital anormalities	Hypocalcemia
		Hypomagnesemia
		Polycythemia

22.4 Diagnosis and classification of disorders of hyperglycaemia in pregancy

SEMDSA endorses and adopts the guideline on the diagnostic criteria and classification of hyperglycaemic disorders first detected in pregnancy as published by the World Health Organisation in 2013.[8]

This guideline:

- Takes into consideration new evidence from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study.
- Proposes a new classification for hyperglycaemia first detected in pregnancy.
- Removes the ambiguity with regard to fasting plasma glucose values in the 1999 WHO guideline.

Classification of diabetes in pregnancy[8]

Pre-existing diabetes
Type 1, type 2 or other form of diabetes that was diagnosed before the pregnancy, with or without complications of diabetes.

Hyperglycaemia first detected in pregnancy
Diabetes mellitus in pregnancy (also referred to as "overt diabetes"): identification of, diabetes for the first time in pregnancy, using the (conventional) 2006 WHO criteria for diabetes in non-pregnant adults. [8]
Gestational diabetes: defined as any degree of glucose intolerance with onset or first recognition during pregnancy[5] that is not clearly overt diabetes, with resolution post-delivery.

Any known type of diabetes mellitus that existed prior to pregnancy should continue to be referred to as such (e.g. type 1 diabetes, type 2 diabetes, LADA etc. [refer to Chapter 2]).

Hyperglycaemia detected for the first time in pregnancy, and at *any stage* of pregnancy, should be classified as either:

- Diabetes mellitus in pregnancy (also referred to as "overt" diabetes by the IASDPG), or
- Gestational diabetes mellitus (GDM).

This consensus distinguishes between "overt" *diabetes in pregnancy* and lesser degrees of hyperglycaemia (GDM) for the following reasons:

- Overt diabetes during pregnancy, whether symptomatic or not, is associated with significant risk of adverse perinatal outcomes
- A detailed assessment for the presence of diabetes-related complications is recommended at diagnosis of overt diabetes (but not GDM), especially complications which can affect pregnancy or be aggravated by it, such as retinopathy and renal impairment
- During pregnancy a more intensive monitoring and treatment of hyperglycaemia is recommended and pharmacotherapy is much more likely to be required to control the hyperglycaemia for patients with overt diabetes
- Following the pregnancy there is a need for closer follow-up and ongoing monitoring and treatment of women with overt diabetes.

The diagnostic criteria are summarised below.

Diagnosis of hyperglycaemia first detected at any stage of pregnancy[8]

Glucose Test	Gestational diabetes	Diabetes mellitus in pregnancy /overt diabetes
Fasting plasma glucose (FPG)	≥ 5.1- 6.9 mmol/l	≥ 7.0 mmol/l; or
One hour post-glucose load (75 g) plasma glucose	≥ 10.0 mmol/l	Not applicable
Two hours post-glucose load (75 g) plasma glucose	≥ 8.5-11 mmol/l	≥ 11.1 mmol/l

One or more of these criteria must be satisfied for the diagnosis of GDM to be made.

22.5 Screening for Gestational diabetes (GDM)

Pregnant women with the risk factors listed below should undergo a two-hour 75 g oral glucose-tolerance test (OGTT) at first booking and if normal, a repeat test at 24-28 weeks gestation**,** to screen for GDM as proposed by IADPSG (International Association of the Diabetes and Study Pregnancy Groups):[5–7]

- Repeated glycosuria
- Previous GDM
- Family history of diabetes (first-degree relative)
- History of stillbirths of unknown origin, previous congenital anomalies and suspicion of polyhydramnios in present pregnancy
- History of high-birth weight infant ≥ 4.5 kg
- Obesity (body mass index (BMI) > 30 kg/m^2)
- History of polycystic ovarian syndrome
- History of unexpected perinatal death
- Women of South-Asian descent

Note: Universal screening for gestational diabetes may be adopted in well-resourced settings.

22.6 Preconception counseling and education

Suitably trained educators should provide education on all aspects of diabetes and its management before and during pregnancy. Pregnancy should ideally be planned in the patient with diabetes and hence preconception counseling is particularly important.

The following topics must be covered:

- Contraception: Effective contraception must be used until optimal HbA_{1C} levels are achieved.
- Optimising glucose control
  - Preconception glycated haemoglobin (HbA_{1C}) must be as close to the normal range as possible without significant hypoglycaemia. Target $HbA_{1C} \leq 6.5\%$.[6,10]
  - Four to seven home blood-glucose tests should be carried out daily; refer to targets below (Table II).
  - If there is suboptimal blood-glucose control on oral agents, refer for insulin therapy.
  - Advice should be given on the management of hypoglycaemia.
- Diet, exercise and structured education:
  - The patient should be referred to a dietitian for education on the ingestion of regular, small-to-moderate portions of low glycaemic-index carbohydrates.
    - Weight-loss education should be provided if the body mass index (BMI) > 27 kg/m^2.
    - Regular exercise should be encouraged.
    - Advice should be given on smoking cessation and abstinence from alcohol use.
- Hypertension
  Chronic hypertensive patients should achieve a satisfactory blood pressure (BP<130/80 mm Hg) pre-conception.[6]
- Medications
  - Ensure folic acid supplementation
  - Review other medication: avoid angiotensin- converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), statins and diuretics.
  - Treat hypertension with methyldopa.
- Screen for and refer diabetic complications e.g. retinopathy, nephropathy and cardiac disease.
- Screen for human immunodeficiency virus (HIV) and immunity to the rubella virus.
- Counsel on risks associated with pregnancy in individuals with diabetes (Table I).

22.7 Management of diabetes during pregnancy

The management of the pregnant diabetic women requires intensive specialist supervision. Referral to a centre with a diabetes-obstetric healthcare team (including a physician with a special interest in diabetes or endocrinology), obstetrician, paediatrician, dietitian and diabetes nurse educator) would be ideal.

The mainstay of the medical management of diabetes during pregnancy involves frequent monitoring of blood glucose levels with adjustment of diet and, in most cases, the addition and or adjustment of therapy to achieve normoglycaemia. Frequent self-monitoring, i.e. six point profiles, of capillary blood glucose must be performed in pregnancy at the following times: pre-meal, one/two hours postprandial, and late at night.[6,7] Continuous glucose monitoring systems (CGMS) should not be offered routinely in pregnant females with diabetes, and may be considered, if available, in the following circumstances:[6]

1. Problematic or severe hypoglycaemia
2. To gain information regarding glucose variability
3. Presence of unstable glucose levels

Patients must be followed closely to term: every two weeks until 32 weeks of gestation, and weekly thereafter until just before delivery.

22.7.1 Dietary therapy during pregnancy

All patients should be referred to a dietician for detailed dietary advice. The diet should comprise approximately 40% carbohydrate (complex, low-glycaemic index, high fibre),[6] 40% fat (at least 50% unsaturated) and 20% protein. The daily meal plan should include three meals, plus three or four snacks. Dietary consistency (in amount and timing of food intake) must be maintained to facilitate tight glycaemic control without inducing hypoglycaemia. Regular, moderate intensity exercise is recommended for at least 30 minutes daily throughout pregnancy.[11] Caution should prevail should any maternal or neonatal complications arise.

22.7.2 Insulin therapy during pregnancy

Insulin is the preferred therapy for diabetes in pregnancy. It is indicated in all patients in whom target blood glucose levels are not met (Table II).

Table II. Target blood glucose levels during pregnancy as adopted by the Endocrine Society[6]

FPG	< 5.3 mmol/l
One hour postprandial	< 7.8 mmol/l
Two-hour postprandial	< 6.7 mmol/l

Multiple injections of short- and longer-acting insulins are recommended, i.e. short-acting human insulin, and intermediate-acting human neutral protamine Hagedorn (NPH) insulin, with the total dose of insulin varying from 0.7 U/kg-2U/kg (present pregnancy weight). Insulin requirements rise progressively as the pregnancy advances. Frequent adjustments to insulin dosages must be made to achieve the target levels of blood glucose (Table II).

Insulin analogues are deemed safe during pregnancy based on a growing body of evidence.[12,13] Short-acting analogues (Aspart and Lispro) are not known to adversely affect the outcomes of the pregnancy or the foetus. To date, there are no clinical trials assessing insulin glulisine in pregnancy and hence it is not recommended.

Long-acting insulin analogues (detemir or insulin glargine) may be continued in women with diabetes who have established good blood glucose control before pregnancy. It should, however, be noted that only insulin detemir is currently approved by the FDA (category B).[14,15]

22.7.3 Oral hypoglycaemic agents in pregnancy

Although there is a lack of long-term safety data for oral hypoglycaemic agents (OHA) in pregnancy, both metformin and glibenclamide may be used in selected patients with type 2 diabetes, overt and GDM (category B). Offer metformin to patients with GDM who have not met glucose targets following 1-2 weeks of dietary and lifestyle manipulation. Consider glibenclamide, for women in whom blood glucose targets are not met with metformin and who decline insulin, or in those patients who are intolerant of metformin.[16,17]

It is important to educate patients regarding the potential risks of each agent and to note that the majority (60-70%) will require supplemental insulin therapy at some point during the pregnancy.[16]

22.8 Timing of delivery

Advise pregnant women with pregestational diabetes and no other complications to have an elective birth, either by induction of labour or caesarean section between 37 and 38 weeks of pregnancy. Consider elective birth prior to 37 weeks if there are metabolic or any maternal or foetal complications.[7] The optimal timing of delivery in patients with GDM has not been evaluated in well-controlled trials.[18]

In controlled patients, whether on diet alone or diet and therapy, pregnancy may continue safely until 39-40 weeks. If any maternal or foetal complications are present, earlier delivery is advised.

22.9 Management during labour or caesarean section

Glycaemic control during labour and birth is of utmost importance to avoid adverse neonatal outcomes. It is essential that capillary blood glucose is monitored hourly during labour and birth, ensuring that it is maintained between 4-7 mmol/l. Intravenous dextrose and insulin infusions should be prescribed at the onset of labour for all diabetic women whose glucose is not maintained between 4-7mmol/l.[6] These infusions are also useful for glycaemic control during caesarian section.

22.10 Postpartum

Women with diabetes in pregnancy should be advised to deliver at a hospital where advanced neonatal resuscitation skills are available. Numerous morbidities may present in babies born to women with diabetes (Table I). A neonatologist should assess newborns for any of these where clinically indicated.

Importantly, insulin requirements fall exponentially after delivery. Caution should be exercised in Type I diabetic patients during this period, in order to avoid hypoglycaemia.

Type 2 diabetic women may resume their OHA immediately post-delivery and be reassured that these agents are safe during breastfeeding. Patients with overt diabetes/GDM and persistent hyperglycaemia immediately postpartum, should be managed accordingly. In those with normal glucose profiles post-delivery, their therapy should be stopped and they should undergo a 75g OGTT at six weeks to check for postpartum persistence of glucose intolerance. If normal, offer an annual HbA_{1c} test, given the high risk of developing Type 2 diabetes in these patients. Lifestyle interventions (diet and exercise) and/or drug therapy, i.e. Metformin, may have a role in preventing future diabetes in such patients.[19,20]

Contraception should be discussed and implemented. Most forms of contraception are safe and effective in women with diabetes.

Breastfeeding should be encouraged wherever possible both in women with overt or gestational diabetes.

Authors: Veronique Nicolau and Kenneth RL Huddle
Editor: Aslam Amod

References

1. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract. 2014;103:176–85.
2. Jiwani A, Marseille E, Lohse N, Damm P, Hod M, Kahn JG. Gestational diabetes mellitus: results from a survey of country prevalence and practices. J Matern Neonatal Med. Taylor & Francis; 2012 Jun 1;25(6):600–10.
3. Macaulay, S. Dunger, D. B. Norris SA. Gestational diabetes mellitus in Africa. PLoS ONE; 2014. 2014;9(6):e97871.

4. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: A Study of Discordant Sibships. Diabetes. 2000;49(12):2208–11.
5. International Association of Diabetes and Pregnancy Study Groups Consensus Panel IA of D and PSGC, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. Diabetes Care. 2010;33(3):676–82.
6. Blumer I, Hadar E, Hadden DR, Jovanovič L, Mestman JH, Murad MH, et al. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(11):4227–49.
7. Diabetes in pregnancy:management from preconception to the postnatal period [Internet]. [cited 2016 Feb 1]. Available from: http://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-from-preconception-to-the-postnatal-period-51038446021
8. World Health Organization. Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy. World Heal Organ. 2013;1–63.
9. Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer a. R, Metzger BE, et al. The Hyperglycaemia and Adverse Pregnancy Outcome Study: Associations of GDM and obesity with pregnancy outcomes. Diabetes Care. 2012;35(4):780–6.
10. Bell R, Glinianaia S V., Tennant PWG, Bilous RW, Rankin J. Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: A population-based cohort study. Diabetologia. 2012;55(4):936–47.
11. Padayachee C, Coombes JS. Exercise guidelines for gestational diabetes mellitus. World J Diabetes July. 2015;25(68):1033–44.
12. Negrato CA, Montenegro Junior RM, Von Kostrisch LM, Guedes MF, Mattar R, Gomes MB. Insulin analogues in the treatment of diabetes in pregnancy. Arq Bras Endocrinol Metabol. 2012;56:405–14.
13. Jovanovic L, Pettitt DJ. Treatment With Insulin and Its Analogs in Pregnancies Complicated by Diabetes.
14. Mathiesen E, Hod M, Ivanisevic M, Duran Garcia S, Brøndsted L, Jovanovic L, et al. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. Diabetes Care. 2012;35(10):2012–7.
15. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin glargine safety in pregnancy: A transplacental transfer study. Diabetes Care. 2010;33(1):29–33.
16. Balsells M, Garcia-Patterson A, Sola I, Roque M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ. 2015;350:h102.
17. Damm P, Mathiesen ER. Diabetes: Therapy for gestational diabetes mellitus—time for a change? Nat Publ Gr. 2015;11(6):327–8.
18. Witkop CT, Neale D, Wilson LM, Bass EB, Nicholson WK. Active compared with expectant delivery management in women with gestational diabetes: a systematic review. Obs Gynecol. 2009;113(1):206–17.
19. Ratner RE, Christophi C a, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab. 2008;93(12):4774–9.
20. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, Remington PL. Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Ann Intern Med. American College of Physicians (190 N. Indenpence Mall West, Philadelphia PA 19106-1572, United States); 2015 Sep 15;163(6):437–51.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 23: Type 2 diabetes mellitus in children and adolescents

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
All children and adolescents with diabetes should be referred to a specialist (an endocrinologist or a specialist with an interest in childhood diabetes) at diagnosis to minimise errors in classification and to plan appropriate management.	C
When there is doubt about the aetiological classification of diabetes in children and adolescents, it is safer to treat for type 1 diabetes until diagnostic clarification can be obtained.	C
Test for anti-GAD and anti-IA2 antibodies in all patients with clinical type 2 diabetes mellitus under18 years of age.	C
Opportunistic screening for Type 2 diabetes mellitus may be considered in the patient at risk and repeated every 2 years.	C
Hyperglycaemic emergencies must be referred to, or managed in conjunction with, a paediatric diabetes specialist.	C
Metformin should be used as first line in the otherwise well, less symptomatic child with type 2 phenotype.	B
Initiate insulin if the HbA_{1C} is not controlled after 6 months.	B
Co-morbidities (hypertension, albuminuria, dyslipidaemia etc.) should be actively sought and treated.	B

In children and adolescents, it can be difficult to differentiate between type 1 and type 2 diabetes mellitus (DM), and both type 1 and type 2 diabetes can manifest in the same individual.[1] Children and adolescents with diabetes are at risk of ketoacidosis, which carries significant morbidity and mortality if not managed appropriately.

23.1 Diagnosing diabetes mellitus in children and adolescents

Children and adolescents may present with the classical symptoms of hyperglycaemia which include polyuria, polydipsia, blurred vision, and weight loss in association with glycosuria, and in some cases, ketonuria.

The criteria for the diagnosis of diabetes in children and adolescents are similar to that in adults and include any one or more of the following four:[1-5]

1. Symptoms of diabetes (polyuria, polydipsia and unexplained loss of weight) and a random plasma glucose of ≥ 11.1 mmol/l

2. Fasting plasma glucose of ≥ 7.0 mmol/l

3. Oral glucose tolerance test using 1.75 g/kg glucose to a maximum of 75 g anhydrous glucose dissolved in water, 2-hour post-challenge plasma glucose ≥ 11.1 mmol/l

4. HbA_{1C} ≥ 6.5%.

In children and adolescents it is *safest to assume that the diagnosis is type 1 DM*, but consider type 2 if any of the following risk factors for type 2 diabetes is present:[1]

- Family history of type 2 diabetes in first-degree or second-degree relative
- High risk race or ethnic group (e.g. South Asians)
- Signs of insulin resistance or conditions associated with insulin resistance (e.g. acanthosis nigricans, hypertension dyslipidaemia, polycystic ovarian syndrome).

Testing for anti-GAD and anti-IA2 antibodies is recommended in all patients with clinical type 2 diabetes mellitus <18 years, as autoimmune beta-cell destruction may co-occur with the insulin resistant features, and obesity/insulin resistance can accelerate the presentation of type 1 diabetes. The presence of antibodies predicts an earlier need for insulin, and the risk of having or developing other autoimmune disorders associated with type 1 diabetes mellitus.[1]

23.2 Screening for type 2 diabetes[1-5]

There is little published evidence to justify systematic screening of asymptomatic children for type 2 diabetes mellitus outside of the research setting.

Opportunistic testing for Type 2 diabetes mellitus should be considered in an overweight patient with:

i) BMI >99th percentile for age and sex, regardless of any additional factors or

ii) BMI at or above the 85th percentile for age and sex and any 2 of the following:

1. Family history of type 2 diabetes in first-degree or second-degree relative.
2. High risk race or ethnic group (e.g. South Asians).
3. Signs of insulin resistance or conditions associated with insulin resistance (e.g. acanthosis nigricans, hypertension dyslipidaemia, PCOS).

General recommendations for screening include**:**

1. Screening should begin at age 10 years, or at onset of puberty if this occurs at a younger age.
2. If the initial screening is normal, repeat testing every 2 years.
3. A fasting plasma glucose test is the preferred screening test.
4. If the fasting glucose does not meet diagnostic criteria but clinical suspicion is high, then an OGTT is a more sensitive tool.

23.3 Management of type 2 diabetes in children and adolescents

The aim of management in children and adolescents with type 2 diabetes mellitus is to minimise the risk of acute and chronic complications of diabetes by:

- Achieving and maintaining weight loss in obese individuals.
- Increasing exercise capacity.
- Normalising blood glucose levels and HbA_{1C} to <7%.
- Controlling associated co-morbidities e.g. hyperlipidaemia and hypertension.

23.3.1 Emergency management

If the child or adolescent presents in diabetic ketoacidosis (DKA) or hyperglycaemic hyperosmolar non-ketotic coma (HHNK), immediately refer the patient to a paediatric diabetes specialist. If this is not possible, contact a paediatric diabetes specialist telephonically for guidance and assistance.

The risk of cerebral oedema and death is high in childhood and adolescence, and a paediatric protocol for management must be used.

23.3.2 Management strategy[1-5]

Best practice: ANY diabetes in a child or adolescent <18yrs should be referred to or discussed with a paediatric diabetes specialist.

There are three components to managing type 2 DM in children and adolescents:

1. Diet/Lifestyle modification
   - The patient and parents must be referred to a dietitian.
2. Medication
   - NB: NO Aspirin is to be used in children and adolescents <21 years.
   - If ketosis, acidosis, or dehydration is present the management is insulin first, adding metformin later once hydrated and ketone-free.
   - If the diagnosis is in doubt whether type 1 or type 2 DM, the management is insulin and metformin, weaning the insulin once the HbA_{1C} is controlled.
   - Ketones (preferably ß-hydroxybutyrate) must be monitored and if they recur, insulin must be reinitiated.
   - Metformin is used in the otherwise well, less symptomatic child with type 2 phenotype.
   - Initiate insulin if the HbA_{1C} is not controlled after 6 months.

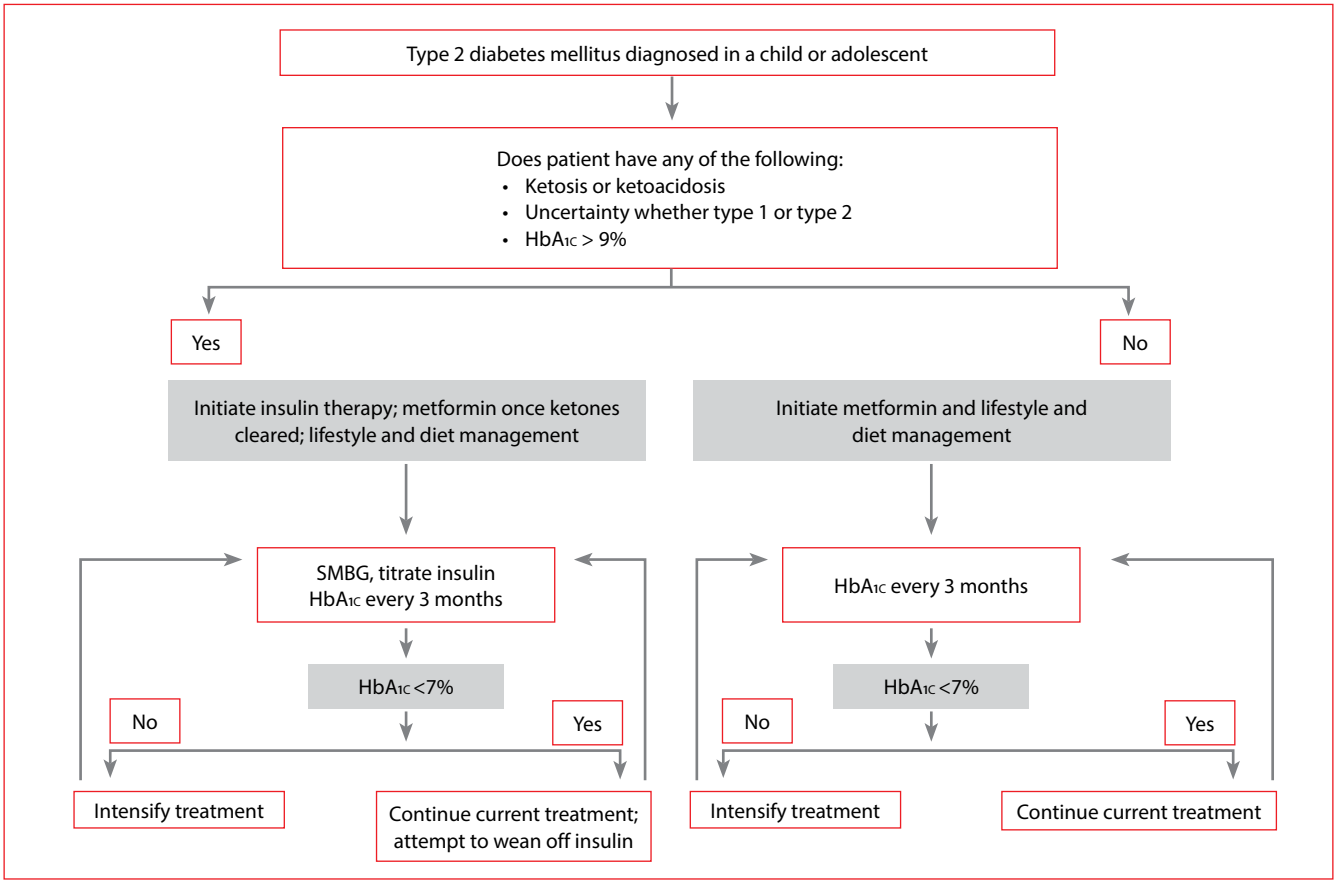
   Metformin initiation: Low dose (500 mg) daily, then twice daily (over 3-4 weeks), then increase dose as tolerated to a maximum of 1 g twice daily, titrated to HbA_{1C} and self-monitoring blood glucose testing (SMBG).
3. Education including SMBG
   - It must be emphasised that there is a possibility that the diagnosis is Type 1 diabetes, and that insulin may be required. SMBG is essential to prevent DKA/HHNK.

Figure I describes the management algorithm with titration thresholds.

23.4 Screening for complications and associated risk factors[1-5]

- **Albuminuria** should be evaluated at diagnosis and annually thereafter. Either micro- or macro-albuminuria may be present at diagnosis. An ACE inhibitor is the first line therapy. Remember to counsel fertile girls/women about the teratogenicity of ACE inhibitors.
- **Hypertension** (>95th percentile for age, height and gender) may be present at or prior to diagnosis of DM and each individual should be assessed at each visit for HPT is estimated to account for 35-75% of diabetes complications i.e. both micro and macrovascular. An ACE inhibitor is first line therapy (especially if microalbuminuria).
- **Dyslipidaemia** is more common in Type 2 DM and in family members and should be screened for when metabolic stability is achieved. Hypertriglyceridaemia and decreased HDLC are hallmarks of Type 2 dyslipidaemia. This is primarily treated with weight loss, lower cholesterol diet and improved glucose control. Statins are only to be used under specialist care – and with extreme caution in childbearing age adolescent girls/young women.
- Evaluate for **non-alcoholic fatty liver disease** (NAFLD) at diagnosis and annually thereafter, with a screening ALT level. Hepatic steatosis is present in 25-45% of adolescents with Type 2 DM. NAFLD now represents the most common cause of cirrhosis in children and is the most common reason for liver transplantation in the adults in the United States. Metformin must not be used if the liver enzymes are >2.5 times the upper limit of normal.
- Screening for **diabetic retinopathy** is to be performed at diagnosis and annually. The preferred method is retinal imaging by fundus photography, or dilated fundoscopy performed by an ophthalmologist or trained clinician.
- A history of pubertal development, menstrual irregularities and obstructive sleep apnoea, should be elicited at diagnosis and regularly thereafter with appropriate management as required.

Figure I: Management algorithm for type 2 diabetes in children and adolescents[2]



Fertility may improve on metformin and contraception should be emphasised in the sexually active individual.

Discuss with or refer to paediatric specialist if any risk factors or complications are present.

Author: Michelle Carrihill, in conjunction with PAEDS-SA

Editors: Ankia Coetzee and Aslam Amod

References

1. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium, Type 2 diabetes in the child and adolescent. Pediatric diabetes 2014:15(suppl. 20):26
2. Copeland KC, Silverstein J, Moore KR, et al. Management of newly diagnosed type 2 diabetes mellitus in children and adolescents. Pediatrics 2013: 2: 131,364
3. Stringer SC, Silverstein J, et al. Management of newly diagnosed type 2 diabetes mellitus in children and adolescents. Pediatrics 2013: 2: 131, e650
4. Executive summary. Type 2 diabetes in children and adolescents. Can J Diabetes 2013; 37: s341
5. NICE. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18) 2015

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 24: Type 2 diabetes in older persons

SEMDSA 2017 Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
A holistic individualised care plan for older individuals, with the aim of maintaining independence should be sought.	C
Prevention of hypoglycaemia should take priority over attainment of glycaemic targets.	C
The healthy older adult who has a life expectancy that exceeds the duration of randomised controlled trials showing benefit, should generally receive diabetes care with goals and targets similar to those for younger adults.	C
Patients older than 65 years should be screened annually for cognitive impairment, dementia and depression because these impact on diabetes management decisions.	B
Metformin is the initial drug of choice for older adults unless contra-indicated or not tolerated.	B
Sulphonylureas should be used with caution as the risk of hypoglycaemia increases exponentially with age. They should be avoided in older adults at particularly high risk for hypoglycaemia or its consequences.	B
Thiazolidinediones should be used with caution due to the risk of fractures and heart failure.	C
DPP-4 inhibitors have excellent tolerability profiles, very low risk of hypoglycaemia and is the preferred second drug for the older person with comorbidities.	B
If insulin mixture is used, premixed solutions and prefilled pens should be used to reduce dosing error.	B
The clock drawing test may be used when assessing capability of a patient to administer insulin.	C

24.1 Introduction

There is no general agreement on the age at which a person becomes old. The common use of chronological age to mark the threshold of old age assumes equivalence with biological age, yet these two are not necessarily synonymous. There is no universally accepted age that defines the older person; the United Nations, World Health Organisation and Statistics South Africa accept age 60+ as being older, while many developed countries use age 65+ (the pensionable age). This chapter will use age 60+ as a basis to define the age at which a progressive decline in health and functional status is more likely to occur, and co-morbidities are likely to be common enough to justify some generalisations about diabetes management. Ageism (discrimination based only on age) is unacceptable. The aim of this chapter is to improve the care of the older person, not to deny care based only on the age of the person.

Ageing is regarded as a major contributor to the diabetes epidemic. The percentage of the South African population aged 60 years and above rose from 7.1% (2.8 million) in 1996 to 8.0% (4.1million) in 2011.[1] Estimates show that the older population will continue to increase, and it is estimated that by 2030 there will be ~7 million older persons in South Africa.[1] The national prevalence of diabetes, hypertension, dyslipidaemia and obesity in 2012 is shown in Appendix 2 (SANHANES-1). For the population older than 65 yrs, 40% have abnormal glucose regulation and 50% have dyslipidaemia.[2] Diabetes in older adults is linked to higher mortality, yet they are often excluded from randomised controlled trials of diabetes.[3,4] The care of older persons with diabetes impacts on the whole family, and this must be taken into account.

Diabetes in older persons is unique and may be complicated by a non- specific clinical presentation with vague symptoms. Age-related insulin resistance (IR) coupled with age-related declines of pancreatic beta-cell function both contribute.[5,6] A small increase in fasting plasma glucose (FPG) and significant increase in post-prandial or 2 hours post oral glucose tolerance test (OGTT) are usually seen. It has also been shown that the renal threshold for glucose increases with age and therefore may not demonstrate glycosuria despite elevated blood glucose.[7] The recommended diagnostic criteria for diabetes remains the same. Caution needs to prevail with the interpretation of the HbA_{1c} as it may be altered by co-existing conditions. These biological differences have important therapeutic relevance to this patient population.

24.2 Hypoglycaemia

Impaired liver and renal function due to ageing, with or without coexisting disease leads to decreased gluconeogenesis. This can be compounded by the reduced clearance of medications such as insulin and sulphonylureas and may put patients at higher risk of hypoglycaemia. The normal (autonomic) defences against

hypoglycaemia may be impaired and can lead to hypoglycaemic unawarenes.[8-10] In addition; hypoglycaemia is hazardous in the older person as it predisposes to falls, cognitive impairment and may precipitate cardiac adverse events.[11] The avoidance of hypoglycaemia should therefore be a priority.

24.3 Glucose targets

Hyperglycaemia is associated with chronic (micro and macrovascular) complications and acute metabolic complications. The general recommendation is to aim for an HbA_{1c} <7.0% based on the results of the UK Prospective Diabetes Study (UKPDS). The UKPDS showed reduction in microvascular complications with glycaemic control but mostly excluded people >65 years.[12] The Veterans Affair Diabetes trial (VADT) included older patients and did show a benefit with a decreased risk of nephropathy with good control. However, like the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial it failed to show cardiovascular benefit.[13] Other trials like the ACCORD (average duration of diabetes 10 years with average age 64 years) found a higher overall mortality in intensively-treated (HbA_{1c} target < 6%) patients.[14] The most reasonable interpretation of the existing evidence is that safe, effective prevention of cardiovascular disease include intensive glycaemic control that begins early in the course of diabetes and that aggressive intensive control in older persons with high cardiovascular risk may be harmful.[15]

When deciding on a treatment plan, it is important to appreciate the heterogeneity of this population and understand the disparities that may exist between individuals of the same chronological age. The principles to be followed in choosing individualised glycaemic targets, including older persons, is discussed in Chapter 8: Glycaemic targets. Healthy older persons should be treated to achieve similar glucose, blood pressure and lipid targets as their younger counterparts.[16] The UKPDS showed benefit of intensive glycaemic control over 10 years, so it is reasonable to aim for intensive control in healthy older persons with a life expectancy greater than 10 years. For older persons with limited life expectancy, cognitive impairment, frailty, high fall risk or multiple comorbidities (e.g. cardiac, renal, respiratory, neurological diseases) less stringent targets (HbA_{1c} up to 8.5% and fasting glucose up to 12 mmol/L) may be acceptable. The prevention of hypoglycaemia should always take priority in these latter patients.

24.4 Specific Treatments

When individualising therapy it is important to contemplate all the potential benefits and harms. Generally medication with the least risk of hypoglycaemia is preferred. Lifestyle modification is still advised and if no contraindication exists, exercise should form part of the treatment plan.

24.4.1 Oral agents

- **Metformin**

  Has evidence for benefit. The dose should be adjusted for renal function. Additional precautions might be necessary at times of severe illness such as dehydration or the use of contrast agents etc.[17,18] Metformin may be associated with biochemical vitamin B12 deficiency in older patients with diabetes mellitus.[19] Its significance is not known but it should be treated. It may also cause undesirable weight loss/cachexia in normal weight individuals; treatment will need to be changed if this occurs.

- **Sulphonylureas**

  Sulphonylureas with active metabolites (glibenclamide and glimepiride) generally have a higher risk of hypoglycaemia. Gliclazide MR is the preferred sulphonylurea as it has the lowest risk of hypoglycaemia (Refer to Chapter 9 for a detailed review). The mean age of patients in the European GUIDE study was 60 yrs and gliclazide MR was 2.5 times less likely to cause significant hypoglycaemia than glimepiride (3.7% vs. 8.9% of patients).[22] The WHO Comparative Safety and Efficacy of Glibenclamide in the Elderly report analysed comparative evidence for safety and efficacy of glibenclamide, glimepiride, glipizide and gliclazide. The evidence showed that glibenclamide was not a safe medication for use in older persons (patients older than 60 years of age).

  Recommendations: Glibenclamide must not be used in older persons.[23] Gliclazide MR has a superior safety profile for hypoglycaemia than glimepiride in a group of patients that included older persons. Initial doses of sulphonylureas should be at half the dose used for adult patients and doses should be increased more gradually.[20-22] When prescribing sulphonylureas in older persons it is best to start at the lowest dose and slowly titrate to individualised target while monitoring for hypoglycaemia. For older individuals at particularly high risk of hypoglycaemia (e.g. HbA_{1c} target <6.5%, renal impairment, erratic food intake, cognitive impairment, hypoglycaemia unawareness) or its consequences (frailty, high fall risk, inability to respond rapidly to symptoms, severe cardiovascular disease, autonomic neuropathy) it is best to avoid the sulphonylureas as a class.

- **DPP-4 inhibitors**

  These oral agents are dosed once-daily. They are weight neutral, have excellent tolerability profiles and pose no risk of hypoglycaemia. As such, they are attractive agents in older persons. They lower HbA_{1c} levels by only 0.6% and are mostly used as add on agents. Not all drugs in this class have the same adverse event profile, and all available agents in SA must be adjusted for renal impairment.[24-26] (See Chapter 9 for details). Their excellent tolerability profiles, low risk of hypoglycaemia, and once-daily dosing make this drug class suitable for the frail and debilitated older persons. Studies by Schweizer et al[27] in populations aged over 75 years and by Strain et al[28] in patients aged over 70 years conclude that vildagliptin is safe in the elderly, and HbA_{1c} targets for control can be achieved safely.

- **Thiazoledinediones**

  The use of pioglitazone in older adults needs to be carefully weighed with the risks of fluid retention, weight gain, and increased risks of heart failure, fracture and possibly bladder cancer.[29] The use of TZDs in patients over the age of 75 is not recommended at primary care level.

- **SGLT2 Inhibitors**

  At the time of publication these drugs were not yet registered in South Africa. Refer to Chapter 9 for a more detailed review. These drugs cause glycosuria resulting in fluid and caloric loss. They do not cause hypoglycaemia. They can result in weight loss, dehydration, hypotension, acute kidney injury and fungal genital infections, and should be avoided in the frail older person. Canagliflozin has been associated with bone fractures and toe amputations. Empagliflozin was associated with reductions in cardiovascular outcomes, death and heart failure in a secondary prevention study, particularly in older people. Patient selection will be important in determining treatment success with this class.

24.4.2 Injectable agents

- **Insulin**

  Prior to initiating insulin it is important to evaluate whether or not the patient is capable of using an insulin pen or drawing up and administering the correct dose. The patient and caregivers should be able to monitor and interpret blood glucose levels. The prescribed insulin regimen should be simple, individualized and have the least risk of hypoglycaemia. The clock drawing test is a screening tool commonly used when screening for dementia. It can accurately be used to predict which older subjects are likely to have problems with insulin therapy.[30-32] Premixed and prefilled insulin pens as alternatives to mixing and conventional syringes are preferred as these have been shown to minimize errors in this group.[33] Detemir and glargine may be used to lower the frequency of hypoglycaemic events.[34,35] The same principles of initiating insulin in general apply, but conservative doses with more conservative glycaemic targets should be used in older persons. (See section on insulin)

- **GLP-1 agonists**

  These are not contra-indicated in overweight older persons but should be used with caution in normal weight older persons because of undesirable weight loss, which may affect muscle bulk strength (sarcopaenia). (See section on non-insulin therapy). Their weight-reducing effect and gastrointestinal side effects may be detrimental for the frail older patients with poor caloric intake and poor nutrition.[36] These drugs should be used with caution in older patients with unintentional weight loss, are malnourished or at high risk for malnutrition.[37] Liraglutide was beneficial in lowering adverse cardiovascular outcomes compared to standard therapies in patients with pre-existing cardiovascular disease in the LEADER trial.[38]

24.4.3 Hypertension

More intensive control of BP (systolic <140 vs. <120) does not improve outcomes and results in more side effects.[39] The target BP for older persons is <140/90 mmHg (see section on hypertension). Drugs with proven benefit in older persons include thiazide-like diuretics (indapamide), ACE-inhbitors and angiotensin receptor blockers and calcium channel blockers, although amlodipine may increase the risk of heart failure.[40]

24.4.4 Dyslipidemia

The treatment of dyslipidaemia with statins for both primary and secondary prevention of CV events has been shown to reduce CV morbidity and mortality in older people with diabetes. The data on the use of fibrates in this patient population are equivocal.[38] Combination statin and fibrate therapy in older persons should only be prescribed under specialist supervision. (Refer to Chapter 16: Cardiovascular Risk and Dylipidaemia.)

Author: Sophia Rauff
Editors: Aslam Amod and Zaheer Bayat

References

1. Census 2011: Profile of older persons in South Africa / Statistics South Africa. Pretoria: Statistics South Africa, 2014
2. Shisana O, Labadarios D, Rehle T, et al. South African National Health and Nutrition Examination Survey, 2012 (SANHANES-1). In: 2014th ed. Cape Town: HSRC Press; 2014:1-397.
3. Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 2003; 51(Suppl. Guidelines):S265–S280
4. Sinclair AJ, Robert IE, Croxson SC. Mortality in older people with diabetes mellitus. Diabet Med.1997; 14:639-647.
5. Amati F, Dubé JJ, Coen PM, Stefanovic-Racic M, Toledo FG, Goodpaster BH. Physical inactivity and obesity underlie the insulin resistance of aging. Diabetes Care 2009; 32:1547–1549
6. Rankin MM, Kushner JA. Adaptive β-cell proliferation is severely restricted with advanced age. Diabetes 2009; 58:1365–1372
7. Butterfield W J, Keen H, Whichelow M J. Renal glucose threshold variations with age. Br Med J 1967; 4 :505
8. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol. 2009; 4(6):1121-1127
9. Shurraw S, Hemmelgarn B, Lin M, Majumdar SR, Klarenbach S, Manns B, et al. Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. Arch Intern Med 2011;171(21):1920-7
10. Tessa Laubscher, Loren Regier, and Julia Bareham. Diabetes in the frail elderly: Individualization of glycemic management Can Fam Physician May 2012 58: 543-546
11. Diabetes Care Program of Nova Scotia. Diabetes guidelines for elderly residents in long-term care. Halifax, NS: Nova Scotia Health; 2010. Available from: http://diabetescareprogram.ns.ca/pdf/LTC/GuideBackground.pdf.
12. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352(9131):837-53. Erratum in: Lancet 1999; 354(9178):602.
13. Veterans Affairs and Department of Defense. VA/DoD clinical practice guideline. Management of diabetes mellitus. Washington, DC: Veterans Affairs and Department of Defense; 2010.
14. ACCORD Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr., Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358(24):2545-59.
15. Barry,HC. Should the target A1C level be less than 7 percent? No: The case for modest glycemic control in patients with type 2 diabetes. Am Fam Physician. 2012 Dec 15; 86(12):1-2.

16. Kronsbein P, Jörgens V, Mühlhauser I, et al. Evaluation of a structured treatment and teaching programme on non-insulin-dependent diabetes. Lancet 1988; 2:1407e11.
17. Breault R, Regier L, Jensen B. Metformin: precautions with renal impairment, hepatic disease and heart failure. Saskatoon, SK: RxFiles; 2008.
18. R.R. Holman, S.K. Paul, M.A. Bethel, D.R. Matthews, H.A. Neil 10-year follow-up of intensive glucose control in type 2 diabetes N Engl J Med, 359 (2008), pp. 1577–1589
19. Adams JF, Clark JS, Ireland JT, Kesson CM, Watson WS. Malabsorption of vitamin B12 and intrinsic factor secretion during biguanide therapy. Diabetologia 1983;24:16-8.
20. Tessier D, Dawson K, Tétrault JP, et al. Glibenclamide vs gliclazide in type 2 diabetes of the elderly. Diabet Med 1994; 11:974e80.
21. Diamicron MR Study Group. Diamicron MR once daily is effective and well tolerated in type 2 diabetes: a double-blind, randomized, multinational study. J Diabetes Complications 2000; 14:185e91.
22. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest 2004; 34:535e42.
23. Chahal A (2011) Comparative safety and efficacy of glibenclamide in the elderly. http://www.who.int/selection_medicines/committees/expert/19/applications/Sulfonylurea
24. Schwartz SL. Treatment of elderly patients with type 2 diabetes mellitus: a systematic review of the benefits and risks of dipeptidyl peptidase-4 inhibitors. Am J Geriatr Pharmacother 2010; 8:405e18.
25. Doucet J, Chacra A, Maheux P, et al. Efficacy and safety of saxagliptin in older patients with type 2 diabetes mellitus. Curr Med Res Opin 2011;27: 863e9.
26. Barzilai N, Guo H, Mahoney EM, et al. Efficacy and tolerability of sitagliptin monotherapy in elderly patients with type 2 diabetes: a randomized, doubleblind, placebo-controlled trial. Curr Med Res Opin 2011;27:1049e58.
27. Schweizer A, Dejager S, Foley JE, Shao Q, Kothny W. Clinical experience with vildagliptin in the management of type 2 diabetes in a patient population ≥ 75 years: a pooled analysis from a database of clinical trials. Diabetes Obes Metab. 2011;13:55-64
28. Strain WD, Lukashevich V, Kothny W, Hoellinger M-J, Paldanius PM. Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy (INTERVAL): a 24 week, randomized, double-blind, placebo-controlled study. Lancet. 2013;382:409-416
29. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone. JAMA. 2010;304(4):411-418.
30. Juby A, Tench S, Baker V. The value of clock drawing in identifying executive cognitive dysfunction in people with a normal Mini-Mental State Examination score. CMAJ. 2002; 167:859-864.
31. Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes selfmanagement and use of care services. Diabetes Res Clin Prac. 2000;50:203-212.
32. Sharon Sundberg, M. (2005). Value of the clock drawing test to predict problems with insulin skills in older adults. Canadian Journal of Diabetes, 29(2), 102.
33. Corsi A, Torre E, Coronel GA, et al. Pre-filled insulin pen in newly insulin treated diabetic patients over 60 years old. Diabetes Nutr Metab 1997;10: 78e81.
34. Coscelli C, Lostia S, Lunetta M, et al. Safety, efficacy, acceptability of a pre- filled insulin pen in diabetic patients over 60 years old. Diabetes Res Clin Pract 1995; 28:173e7
35. Garber AJ, Clauson P, Pedersen CB, Kolendorf K. Lower risk of hypoglycemia with insulin detemir than with neutral protamine hagedorn insulin in older persons with type 2 diabetes: a pooled analysis of Phase III trials. J Am Geriatr Soc 2007; 55:1735-40.
36. Soe K, Sacerdote A, Karam J, Bahtiyar G. Management of type 2 diabetes mellitus in the elderly. Maturitas. 2011; 70(2):151–159.
37. Neumiller JJ, Setter SM. Pharmacologic management of the older patient with type 2 diabetes mellitus. Am J Geriatr Pharmacother. 2009; 7(6):324–342.
38. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827.
39. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013; 37(suppl 1):S1-S212.
40. Whelton PK, Barzilay J, Cushman WC, et al, ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALL-HAT). Arch Intern Med 2005;165:1401e9.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 25: HIV and diabetes

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations
Both HIV and diabetes are increasing epidemics and each condition influences the other.
HIV itself, and the treatment of the condition, both increase the risk for the development of diabetes.
The criteria for the diagnosis of diabetes in HIV-infected individuals is not different. However, HbA_{1C} measurements may be influenced by co-morbidities and drugs, and is therefore not optimal for diagnosis. A glucose tolerance test is preferred for diagnosis. HbA_{1C} is suitable for diabetes monitoring.
Metabolically neutral anti-retroviral drugs are preferred in patients with diabetes.
Metfomin, pioglitazone, sulphonylureas and insulin are all effective in the treatment of diabetes in patients infected with HIV infection, although caution is needed with specific co-morbidities.

25.1 Introduction

South Africa, with a population of just over 50 million people, has an HIV prevalence of 12.7%, equating to about 7.03 million people living with HIV, which is the highest in the world, and equally has the largest state funded Anti HIV Roll out programme, with approximately 3.4 million patients receiving treatment. This has translated into a reduction in acute complications of HIV infection and increased longevity, with lifespan increases from 52 years in males in 2002 to 60.6 years in 2016 and 56.4 years to 64.3 years for females for the same period.

This has led to an increase in the chronic metabolic complications of both HIV and highly active anti-retroviral therapy (HAART) which amongst others include dyslipidaemia, accelerated atherosclerosis, osteoporosis, insulin resistance and diabetes mellitus.

In patients treated with HAART, the prevalence of new onset diabetes mellitus is approximately 5% and that of pre diabetes up to 15%, especially in patients on protease inhibitors (PI) and certain nucleoside reverse transcriptase inhibitors (NRTI).

25.2 Metabolically neutral vs. metabolically unsafe drugs

Since the last type 2 diabetes guidelines were published in 2012, the South African HIV Society has adopted new treatment guidelines in line with international guidelines. The biggest change is the so-called "test to treat" strategy whereby every HIV positive patient is initiated on HAART irrespective of their CD4 cell count or clinical condition. This means that more patients are becoming eligible for treatment. However, an even bigger positive step is the introduction of newer, safer, metabolically neutral antiretroviral drugs as illustrated below (Table I).

The newer classes which include entry inhibitors (enfurvirtide), and integrase inhibitors (raltegravir) and CCR5 inhibitors (maraviroc) are considered metabolically neutral. Therefore it is likely that more patients will live longer with safer drugs.

25.3 Risk factors for development of diabetes in HIV+ patients

There are many factors that predispose HIV positive patients on HAART to developing diabetes. The same traditional risk factors that apply to non-HIV positive patients must still be considered.

25.3.1 Traditional risk factors

- Family history
- Ethnicity
- Obesity (BMI ≥25 kg/m^2)
- Physical inactivity
- Previous gestational diabetes or big baby (>4 kg)

Table I: Classification of drug classes by metabolic profile

Metabolically neutral NRTIs	Metabolically unsafe NRTIs	Metabolically unsafe Protease Inhibitors	Metabolically neutral Protease Inhibitors
Abacavir	Stavudine	Indinavir	Darunavir
Tenofivir	Didanosine	Ritonavir	Atazanvir
Emtricitabine	Zidovudine	Saquinavir	
Lamivudine		Lopinavir	
		Ritonavir	

- Cardiovascular disease
- Low birth weight
- Polycystic ovary syndrome or acanthosis nigricans
- Dyslipidaemia
- Age > 45 years

25.3.2 HIV related risk factors

- HIV virus, viral load, CD4 count, duration of HIV infection
- Rapid weight gain after the catabolic phase (return to health phenomenon)
- Co infection with hepatitis
- Dyslipidaemia with lipotoxicity
- Lipodystrophy
- Iatrogenic

25.4 Classification of HIV in patients with diabetes

Three subgroups of patients with HIV and diabetes can be identified:

1. Patients with pre-existing diabetes who contract HIV.
2. Those who are diagnosed with both HIV and diabetes mellitus at the same time.
3. Those who develop hyperglycaemia post-HAART initiation.

25.5 Mechanisms of diabetes in HIV infected individuals

HIV viral infection, through various inflammatory mediators and cytokines, can induce a state of insulin resistance. Most cases of HIV-associated diabetes are type 2 diabetes. Auto-immune ß cell destruction has also been described.

Co–infection with hepatitis C (HCV) has been shown to cause dysglycaemia by increasing intrahepatic tumour necrosis factor and causing hepatic steatosis. Hepatitis C positive patients above the age of 40 years are three times more likely to develop DM than those without.

Return to health phenomenon: as a patient's general health improves, there is a rapid increase of body fat (visceral fat) instead of lean muscle mass that they would have lost during the catabolic phase of the disease. This can overwhelm the β cell secretory capacity leading to β cell failure.

Drugs (iatrogenic)

NRTI's: These drugs can cause mitochondrial toxicity with subsequent lipoatrophy and therefore reduced uptake of triglyceride and glucose in affected tissues. Stavudine has the highest onset of diabetes relative risk per year of exposure followed by zidovudine and didanosine. This class may also cause pancreatitis.

NNRTI's: Have not directly been implicated in the pathogenesis of diabetes. They might however induce dyslipidaemia in the form of raised triglycerides.

Protease Inhibitors: Are the biggest diabetogenic culprits, inducing hyperglycaemia by different mechanisms which include but are not limited to:

1. Reducing insulin production by between 25-50% by the β cells.
2. Impairing GLUT-4 translocation to the surface of the cell membrane and therefore preventing entry of glucose into cells.
3. Inhibiting PPARy receptors and therefore preventing adipocyte differentiation with resultant release of free fatty acids.
4. Inducing lipodystrophy – the exact mechanism of lipodystrophy remains unknown with some theories implicating mitochondrial dysfunction with increased fat cell apoptosis, and others suggesting inhibition of SREBP–I activation of RXR-PPARy heterodimers in adipocytes. Clearly not one mechanism can explain its pathogenesis.

25.6 Screening

1. All HIV positive patients with traditional diabetes risk factors should be screened as in non-HIV positive patients.
2. HIV positive patients should be screened before initiating HAART or when changing ARV's.
3. Every 3-6 months for patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).
4. Annually if initial glucose levels were normal at the initial screen.
5. Fasting plasma glucose is preferred but standard 75 g OGTT is preferred in those with IGT or IFG with additional risk factors

25.7 Diagnosis of diabetes in HIV

The same diagnostic criteria apply as in non-HIV positive patients. Caution is advised when using HbA_{1C} for diagnosis as it might be affected by multiple variables which include drugs (AZT), presence of anaemia, and opportunistic infections involving the bone marrow. Most authorities do not recommend the use of HbA_{1C} for diagnosis in people with HIV infection but it remains the gold standard for monitoring. The target for HbA_{1C} should be individualised based on the patient's general condition.

25.8 Evaluation of a patient

Initial evaluation of a patient with both HIV and diabetes mellitus includes a detailed history which amongst others includes a detailed search for infections which are common in both conditions and that includes search for tuberculosis, fungaemia, sexually transmitted infections, urinary tract infections and presence of hypertension, renal impairment and any form of dyslipidaemia, as these need to be aggressively managed and will also influence the choice of anti HIV drugs.

Initial investigations should include:

1. Full blood count
2. Urea and creatinine with estimated GFR
3. Liver function with hepatitis screen
4. CD4 count
5. Viral load
6. HbA_{1C}
7. Serum lipids

Depending on the initial examination, the treating practitioner will decide on the need for further investigations, such as chest radiograph, blood or urine cultures, or any other imaging techniques.

25.9 Monitoring of diabetes control in patients with HIV infection

Glycaemic control in patients with both diabetes and HIV infection is no different from non-HIV infected patients; however, caution is needed in the interpretation of HbA_{1C} as a number of HIV-specific factors may influence this value (See Chapter 3 and Appendix 3).

25.10 Treatment of diabetes in HIV infected individuals

25.10.1 General measures

1. Appropriate treatment of opportunistic infections.
2. Lifestyle modification, which includes physical exercise, smoking and alcohol cessation and where available, dietary advice, taking account of BMI, desired weight and co-morbidities.
3. Psychosocial support and both family and community involvement where feasible.
4. Reinforce compliance at every visit.
5. Treatment of other cardiovascular risk factors:

    a. Dyslipidaemia – general measures and targets apply; the only major exception is that simvastatin is contraindicated in patients using protease Inhibitors as it competes for the same Cytochrome P450 Isoenzyme. Fluvastatin and pravastatin are safer.

    b. Hypertension – ACE Inhibitors and ARB's (Angiotensin Receptor Blockers) need to be used with caution: captopril has been associated with the development of Kaposi's sarcoma and enalapril may cause myalgias and diarrhoea. In addition, ARB's may compete with other drugs that are metabolised by cytochrome P450 Isoenzymes.

25.10.2 Glucose lowering drugs

a. Insulin sensitizers: Pioglitazone

Thiazolidinedione's (TZDs) –Pioglitazone has a mechanism of action that is favourable in patients with HIV and diabetes. Pioglitazone may be a drug of choice in patients with lipoatrophy as it has been showed to cause fat redistribution from abdominal fat to subcutaneous fat in lipoatrophic areas. Pioglitazone should not be used with tenofovir as the risk of osteoporotic fractures increases.

b. Biguanides

Metformin still remains the drug of choice for most patients with HIV. It should, however, be used with caution in patients with HIV associated enteropathy as the gastrointestinal side effects of metformin will be exaggerated. It is contraindicated in patients with HIV associated nephropathy (HIVAN), liver disease, cachectic patients and tuberculosis as the risk of lactic acidosis is markedly increased. It should not be used in conjunction with thymidine-based NRTI's (Stavudine, didanosine) as the risk of lactic acidosis is increased due to mitochondrial toxicity. Extended release metformin is the preferred formulation of the drug

c. Insulin secretagogues

Sulphonylureas

The general principles apply as in non-HIV patients, but, caution has to be exercised in patients with cachexia who might have depleted glycogen stores and who are at increased risk of hypoglycaemia. Where possible, modified release formulations should be used.

Glinides

Because of their short acting profile and lower risk of hypoglycaemia, they are suitable drugs but are not commonly used in South Africa.

d. Incretins

There is currently no data available regarding the newer classes of drugs in HIV patients with diabetes, including DPP-4 inhibitors and incretin receptor analogues.

e. Insulin

Insulin remains the drug of choice for most patients with HIV and diabetes and ultimately most, if not all patients, will require insulin because of the progressive nature of the disease. Insulin has anabolic effects, reduces inflammatory markers, has no interactions with antiretroviral drugs and can be used safely in patients with renal failure (with proper titration).

Refer to general guidelines on insulin initiation and titration. It is important to note that insulin requirements might initially be high and will later fall as glucotoxicity is reversed and infections are controlled.

25.10.3 Changing HAART

A patient who develops diabetes while on HAART with drugs that are potentially diabetogenic especially the protease inhibitors should be changed to anti-retroviral agents that are metabolically neutral (see Table I).

Author: Duma Khutsoane
Editors: Fraser J Pirie and Aslam Amod

References

1. The National Department of Health, South Africa. National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults. 2015.
2. Calza L. Manfred R, Chiodo F. Insulin resistance and diabetes mellitus in HIV infected patients receive antiretroviral therapy. Metabolic Syndrome Related Disorders 2004; 4(4): 241-250.
3. Grinspoon S. Mechanism and strategies for insulin resistance in acquired immune deficiency syndrome. Clinical Infectious Diseases 2003; 37: Supplement 2 S85-90.
4. Kalra S, Kalra B, Agrawal N, Unnikrishnan AG. Understanding diabetes in patients with HIV/AIDS. Diabetology & Metabolic Syndrome. 2011; 3(2). Available online: https://dmsjournal.biomedcentral.com/articles/10.1186/1758-5996-3-2 Accessed 19 April 2017.

5. Samaras K. Metabolic consequences and therapeutic options in highly active antiretroviral therapy in human immunodeficiency virus -1 infection. The Journal of Antimicrobial Chemotherapy. 2008; 61(2): 238-245.
6. American Diabetes Association. Standards in the medical care of diabetes - 2017. 2017.
7. Diabetics Australia. Australian diabetic guidelines. 2016; Available online: https://www.diabetesaustralia.com.au/best-practice-guidelines Accessed 19 April 2017.
8. South African National AIDS Council. South Africa's National Strategic Plan on HIV, TB and STI's 2017-2022. 2017; Available online: http://nsp.sanac.org.za/ Accessed 19 April 2017.
9. Vigouroux C, Maachi M, Nguyen TH, et al. Serum adipocytokines are related to lipodystrophy and metabolic disorder in HIV-infected men under antiretroviral therapy. AIDS. 2003; 17: 1503-1511.
10. Florescu D, Kotler DP. Insulin resistance, glucose intolerance and diabetes mellitus in HIV infected patients. Antiviral Therapy. 2007; 12:149-162.
11. Aboud M, Elgalib A, Kulasegaram R, Peter B. 2007 Insulin resistance and HIV infection: a review. International Journal of Clinical Practice. 2007; 61:463-472.
12. Zandman-Goddard G, Shoenfeld Y. HIV and autoimmunity. Autoimmunity Reviews. 2002; 1:329-337.
13. Kobayashi T, Tamemoto K, Nakanishi K, Kato N, Okubo M, Kajio H, Sugimoto T, Murase T, Koska K. Immunogenetic and clinical characterization of slowly progressive IDDM. Diabetes Care. 1992; 16:780-788.
14. Friis-Moller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, Thiebaut R, Morteldt L, De Wit S, Pradier C, Calvo G, L aw MG, Kirk O, Phillips AN, Lunggren JD. Data collection on Adverse Events of Anti HIV drug (DAD) Study Group: Combination antiretroviral therapy and the risk of myocardial infarction. The New England Journal of Medicine. 2003; 349(21):1993-2003.
15. Brown TT, Cole SR, Li X, Kingsley LA, Palella FJ, Riddler SA, Visscher BR, Margolick JB, Dobs AS: Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicentre AIDS co-host study. Archives of Internal Medicine. 2005; 165:1179-1184.
16. Freire E. Overcoming HIV-1 resistance to protease inhibitors. Drug Discovery. 2006; 3(2): 281-286.
17. Kruger A, Greeff M, Watson MJ, Fourie CMT. Health care seeking behaviour of newly diagnosed HIV infected people from rural and urban communities in the North-West province of South Africa. African Journal of Nursing and Midwifery. 2009; 11(2): 30-47.
18. Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S, PURE Investigators-Writing Group. The Prospective Urban Rural Epidemiology (PURE) study: Examining the impact of societal influences on chronic noncommunicable disease in low-, middle-, and high –income countries. American Heart Journal. 2009; 158: 1-7.
19. Lee GA, Rao M, Grunfeld C: The effects of HIV Protease inhibitors on carbohydrate and lipid metabolism. Current Infectious Disease Report. 2004; 6:471-482.
20. Feigenbaum K, Longstaff L: Management of the metabolic syndrome in patients with human immunodeficiency virus. The Diabetes Educator. 2010; 36(3):457-464
21. Fitch KV, Anderson EJ, Hubbard JL, Carpenter SJ, Waddell WR, Caliendo AM, Grinspook SK. Effects of life style modification programs in HIV infected patients with metabolic syndrome. AIDS. 2006; 20(14):1843-1850.
22. Robinson FP, Quinn LT, Rimmer JH: Effects of high-intensity endurance and resistance exercise on HIV metabolic abnormalities: a pilot study. Biological Research for Nursing. 2007; 3:177-185.
23. Samaras K. Prevalence and pathogenesis of diabetes mellitus I HIV-1 infection treated with combined antiretroviral therapy. The Journal of Acquired Immune Deficiency Syndromes. 2009; 50: 499-505.
24. Saves M, Raffi F, Capeau J, Rozenbaum W, Ragnaud JM, Perronne C, Basdevant A, Leport C, Chêne G; Antiprotéases Cohorte (APROCO) Study Group. Factors related to lipodystrophy and metabolic alterations in patients with human immunodeficiency virus infection receiving highly active antiretroviral therapy. Clinical Infectious Diseases. 2002; 34: 1396-1405.
25. Hadigan C, Meigs JB, Corcoran C, Rietschel P, Piecuch S, Basgoz N, Davis B, Sax P, Stanley T, Wilson PW, D'Agostino RB, Grinspoon S. Metabolic abnormalities and cardiovascular disease risk factors in adult with human immunodeficiency virus infection and lipodystrophy. Clinical Infectious Diseases. 2001; 32:130-139.
26. De Wit S, Sabin CA, Weber R, et al. Incidence and risk factors for new –onset diabetes in HIV infected patients: the data collection on adverse events of anti HIV drugs (DAD) study. Diabetes Care. 2008; 31: 1224-1229.
27. Fleischman A, Johnsen S, Systrom DM, Hrovat M, Farrar CT, Frontera W, Fitch K, Thomas BJ, Torriani M, Côté HC, Grinspoon SK. Effects of a nucleoside reverse transcriptase inhibitors, stavudine, on glucose disposal and mitochondrial function in muscle of health adults. American Journal of Physiology, Endocrinology and Metabolism. 2007; 292: E1666-1673.
28. Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C, Godfrey C, Jahed NC, Myers L, Katzenstein D, Farajallah A, Rooney JF, Pappa KA, Woodward WC, Patterson K, Bolivar H, Benson CA, Collier AC; AIDS Clinical Trials Group Study A5202 Team. Atazanavir plus ritonavir or efavirenz as part of a 3 –drug regimen for initial treatment of HIV-1. Annals of Internal Medicine. 2011; 154:445-456.
29. SEMDSA. SEMDSA guidelines for diagnosis and management of type 2 diabetes mellitus in primary health care in South Africa. 2012.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Chapter 26: Management of diabetes during Ramadan

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Fasting during the month of Ramadan may pose a health risk to some patients with diabetes. The healthcare professional should assess this risk according to the risk categories defined by medical experts and Islamic jurists, that serve as a guidance as to who could or should not fast.	C
For those patients who intend to fast despite medical advice to the contrary, the role of the healthcare professional is to advise the patient on how to fast as safely as possible.	C
A pre-Ramadan medical assessment is essential to assess overall wellbeing, define co-morbidities, provide Ramadan-focussed education on meal planning, adjustments to medication, planning of exercise and monitoring of blood glucose.	C
Always enquire about the patient's previous challenges and successes during Ramadan to guide treatment decisions.	C
Patients must be educated that fingerprick self-monitoring of glucose does not invalidate the fast.	C
Patients must be educated to break their fast if they have any confirmed or suspected hypoglycaemia irrespective of the time of day.	C
DPP-4 inhibitors are preferred to sulphonylureas as they have a lower potential to cause hypoglycaemia, although both may be used during Ramadan.	B
GLP 1 analogues may be safely used provided they are started one to two months prior to Ramadan.	B
Insulin doses, timing and regimens need to be modified during Ramadan.	C
Patients must be educated about self-titration and adjustment of insulin during fasting to enable individuals to fast safely during Ramadan.	C

26.1 Introduction

Fasting during the holy month of Ramadan constitutes one of the five fundamental pillars of Islam. Muslims abstain from food and drink from dawn (suhur) to dusk (iftaar). Despite ill individuals being exempted from this obligation, many Muslims with diabetes mellitus will still wish to fast. Individuals with diabetes that fast are at risk for hypoglycaemia, hyperglycaemia and dehydration. It is increasingly important that healthcare professionals (HCP) are aware of potential risks associated with fasting in Ramadan, and adopt the necessary approach to mitigate those risks.

This section outlines defining criteria for diabetic subjects who may safely fast during Ramadan, emphasises the importance of planning and education before Ramadan, and provides guidelines on dietary advice and adjustments that need to be made at a therapeutic level to minimise the risks associated with fasting during Ramadan.

The terms suhur and iftaar are used throughout this guideline. Suhur refers to the pre-dawn meal at the start of the day's fast and will be referred to as "pre-dawn meal" or "morning meal". Iftaar refers to the meal at sunset and marks the end of the day's fast; it will be referred to as "sunset meal" or "evening meal". Individuals observing the fast are prohibited, *inter-alia*, from smoking and consuming any food or liquid orally.

26.2 Ramadan and fasting

"O you who believe! Fasting is prescribed to you as it was prescribed to those before you so that you may attain self restraint".[1]

"Whoever witnesses the month (of Ramadan) then he/she should fast. But, if any of you is ill or travelling – then he or she is exempted from fasting".[2]

Fasting in the month of Ramadan is one of the five pillars of Islam. It is incumbent on every Muslim upon attaining puberty and thereafter to fast during this month. However, certain categories of individuals are exempted from fasting e.g. an ill person, a traveller or a pregnant or lactating woman.[1] Missed fasting days need to be made up once an individual regains sound health.

26.2.1 Fasting exemptions

The month of Ramadan involves greater expression of devotion in addition to fasting in order to achieve nearness to and seek the pleasure of God, with the result that many Muslims who are exempt from fasting because of diseases such as diabetes are reluctant to take advantage of this concession.

Islamic scholars and medical experts have made recommendations for "diabetes and fasting of Ramadan",[3] which may help individuals with diabetes make an informed decision. Patients with diabetes are classified into 3 categories: - very high risk, high risk and moderate to low risk (Table I).

26.3 Pre-Ramadan assessment

Assessments for risk stratification and a focussed education plan for all Muslim patients with diabetes should occur six to eight weeks prior to Ramadan. Based on the evaluation, the HCP should advise on fasting. Patients can be reassured that these stratified risk recommendations have been endorsed by religious leaders and scholars. Those in the exempt category who insist on fasting should be reminded of the Quranic injunction: "Let not your own hands throw you into destruction".[4]

For fasting individuals, it is essential for the HCP to assist with an individualised management plan, focusing on symptoms of hypoglycaemia or hyperglycaemia, importance of self-monitoring of blood glucose (SMBG), Ramadan nutrition, modification of therapy and management of comorbidities. It should be emphasised that blood glucose monitoring via pinprick does not break the fast. For those individuals who are not fasting, the HCP should still provide education on appropriate Ramadan nutrition as dietary habits often change during the month.

26.3.1 Ramadan Nutrition Plan

Meals must be planned to avoid hypoglycaemia, dehydration and postprandial hyperglycaemia. Dietary plans should be developed based on individual metabolic, nutritional and lifestyle requirements. A balanced diet which differs little from the normal everyday diet is advised, limiting foods usually high in sugar and fat i.e. the fast should not be followed by feasting but rather by several smaller meals during the period between iftaar (evening) and suhur (morning). The pre-dawn meal should never be missed. The daily calorie allowance can be split over two to three smaller meals during the non-fasting interval. Dates, the traditional food used to break the fast, are high in sugar and

Table I: Pre-Ramadan Assessment and Risk Stratification

Risk category Religious opinion	Patient characteristics	Comments
Category 1: very high risk Listen to medical advice MUST NOT fast	One or more of the following: • Severe hypoglycaemia within the three months prior to Ramadan • DKA within the three months prior to Ramadan • Hyperosmolar hyperglycaemic coma within the three months prior to Ramadan • History of recurrent hypoglycaemia • History of hypoglycaemia unawareness • Poorly controlled T1DM • Acute illness • Pregnancy in pre-existing diabetes, or GDM treated with insulin or SUs • Chronic dialysis or CKD stage 4 & 5 • Advanced macrovascular complications • Old age with ill health	If patients insist on fasting then they should: • Receive structured education • Be followed by a qualified diabetes team • Check their blood glucose regularly (SMBG) • Adjust medication dose as per recommendations • Be prepared to break the fast in case of hypo- or hyperglycaemia • Be prepared to stop the fast in case of frequent hypo- or hyperglycaemia or worsening of other related medical conditions
Category 2: high risk Listen to medical advice SHOULD NOT fast	One or more of the following: • T2DM with sustained poor glycaemic control* • Well-controlled T1DM • Well-controlled T2DM on MDI or mixed insulin • Pregnant T2DM or GDM controlled by diet only or metformin • CKD stage 3 • Stable macrovascular complications • Patients with comorbid conditions that present additional factors • People with diabetes performing intense physical labour • Treatment with drugs that my affect cognitive function	If patients insist on fasting then they should: • Receive structured education • Be followed by a qualified diabetes team • Check their blood glucose regularly (SMBG) • Adjust medication dose as per recommendations • Be prepared to break the fast in case of hypo- or hyperglycaemia • Be prepared to stop the fast in case of frequent hypo- or hyperglycaemia or worsening of other related medical conditions
Category 3: moderate/ low risk Listen to medical advice Decision to use licence not to fast based on discretion of medical opinion and ability of the individual to tolerate fast	Well-controlled T2DM treated with one or more of the following: • Lifestyle therapy • Metformin • Acarbose • Thiazolidinediones • Second-generation SUs • Incretin-based therapy • SGLT2 inhibitors • Basal insulin	Patients who fast should: • Receive structured education • Check their blood glucose regularly (SMBG) • Adjust medication dose as per recommendations

*Level of glycaemic control to be agreed between physician and patient, according to multiple factors
CKD, chronic kidney disease; DKA, diabetic ketoacidosis; GDM, gestational diabetes mellitus; MDI, multiple dose insulin; SMBG, self-monitoring of blood glucose; SU; sulphonylurea; T1DM, type 1 diabetes; T2DM, type 2 diabetes

only two or three should be consumed. Adequate water and low-calorie drinks should be consumed in the non-fasting period to reduce risk of dehydration, and caffeine-containing beverages should be limited or avoided.

Dietary macronurient composition must be individualised with a nutritional approach that limits energy from fat (< 30%) and saturated fat (<10%), increases fibre (>15g/1000 kcal) and promotes whole grain, unrefined carbohydrates instead of refined carbohydrates. Simple carbohydrate consumption should be limited to small quantities at iftaar (sunset meal), if at all. Country-specific meal plans have been developed for different regions based on the caloric requirements and specific habits of a region. Appendix 26 provides country-specific meal plans appropriate for South Africa.

26.4 Monitoring of blood glucose

SMBG is important to enable safe fasting as both hyperglycaemia and hypoglycaemia are risks associated with fasting. It must be emphasised that finger prick glucose testing does not invalidate the fast. The low risk patient may test his glucose once or twice daily either at iftaar or midday. The high risk patient is usually on insulin and it is recommended that glucose levels are monitored prior to suhur and iftaar as well as mid-morning and mid-afternoon. In addition, testing is done whenever hypoglycaemia is suspected. A two (2) hour post iftaar test may be useful to detect hyperglycaemia. Patients must receive an adequate supply of test-strips before and during Ramadan.

26.5 Non-insulin therapies

There is a paucity of well designed, randomised controlled trials assessing the efficacy, tolerability and safety of the various oral glucose lowering drugs (GLDs) when used in Ramadan. The emergence of DPP 4 inhibitors has led to several studies assessing the role of these agents during the Ramadan fast, especially comparing them to sulphonylureas.

26.5.1 Metformin

Metformin is the preferred agent for managing patients with type 2 diabetes mellitus. Metformin carries a very low risk of hypoglycaemia[4], making it an attractive option for individuals who fast. There are no RCTs looking specifically at the safety and efficacy of metformin as monotherapy during Ramadan. However, most trials of other GLDs have used metformin as background medication, and no safety issues have been identified.

As metformin appears to be safe, dose modification is probably unnecessary. Some suggestions, if individuals choose to make dose adjustments, include dividing the total daily dose as follows: -

- Two thirds at iftaar (evening meal), one third at suhur (morning meal).
- Once daily metformin extended-release should be taken at iftaar (evening meal) rather than at suhur.

26.5.2 Acarbose

No data are available for the use of acarbose as monotherapy in prolonged fasting, although one study comparing it to vildagliptin as monotherapy showed similar glycaemic reduction but poorer tolerability.[6] Dose adjustment is not required.

26.5.3 Oral short acting insulin secretagogues (meglitinides)

Studies comparing use of these agents with sulphonylureas showed either no difference[7] or improved[8] glycaemic control, and no difference[9] or lower risk[7,10] of hypoglycaemia. The glinides (eg. repaglinide) are short acting but are more expensive and, like sulphonylureas, are associated with weight gain. They can be taken twice daily with meals.

26.5.4 Thiazolidinediones

A study comparing pioglitazone use to placebo in Ramadan showed improved glycaemic control, significantly greater weight gain and no increase in hypoglycaemia.[9] No adjustments of thiazolidinedione dose is necessary, but consider administering the drug at iftaar (evening). Peak onset of action is 10-12 weeks so therapy should be initiated in advance.

26.5.5 Sulphonylureas

Sulphonylureas vary in their propensity to cause hypoglycaemia, with much lower rates seen with some second generation agents. The use of gliclazide is associated with comparably lower rates of hypoglycaemia, although the modified release preparation has been less well studied in Ramadan. Switching a once daily dose of glimepiride or gliclazide to iftaar (evening) as opposed to suhur (morning) showed no change in glycaemic control[11,12] or weight,[12] and either no change[11] or fewer[12] hypoglycaemic episodes compared to pre-Ramadan. Comparison of a DPP-4 inhibitor sitagliptin to sulphonylurea use in Ramadan showed more hypoglycaemia with sulphonylureas in general but similar rates with gliclazide.[13] A meta-analysis of three randomised controlled trials comparing gliclazide to DPP-4 inhibitors showed no statistical difference in the rates of symptomatic hypoglycaemia.[14]

Consider the following dose adjustments:

- If taking a single daily dose, consider a switch to iftaar (evening).
- If taking the drug twice daily, reduce the morning dose by 50%. eg. change a twice daily dose of gliclazide 80 mg to 40 mg at suhur (morning) and 80 mg after Iftaar (evening). If taking a higher dose in the morning, take the morning dose at iftaar (evening) and take half the evening dose at suhur (morning).

Gliclazide modified-release is the sulphonylurea of choice because of its consistently better safety profile (Refer to Chapter 9). Glibenclamide must not be used.

26.5.6 DPP-4 inhibitors

A meta-analysis of DPP-4 inhibitor use compared to sulphonylureas as a group showed similar glycaemic efficacy but lower rates of hypoglycaemia in Ramadan.[15] Studies using vildagliptin compared to gliclazide show comparable

glycaemic efficacy,[16,17] no difference in weight[17,18] and less hypoglycaemia[16,17,18] which was not always significant. DPP-4 inhibitors are an alternative to sulphonylureas if the risk of hypoglycaemia is high.

If appropriate, consider switching to this class prior to Ramadan.

- No dosage adjustments are necessary but if taking a once daily dose, switch to iftaar (evening).

26.5.7 SGLT 2 Inhibitors

There is little data available for use of these drugs in Ramadan. These agents are associated with a low risk of hypoglycaemia when used as monotherapy in non-fasting individuals. Concerns have been raised about ketoacidosis, and it is important to recognise the potential risk for dehydration, particularly in the elderly, with concomitant diuretic use and also with prolonged fasting in warm or humid climates.

- Consider switching daily dose to iftaar (evening).

26.5.8 Glucagon–like peptide-1 agonists

A glucagon-like peptide-1 (GLP-1) agonist can be used safely during Ramadan in combination with metformin[19,20] as well as with sulphonylureas and insulin.[21] Although there are no studies with exenatide, liraglutide has been safely used in Ramadan with stable glycaemic control, weight loss and a trend to lower rates of hypoglycaemia when compared to sulphonylureas.[1,2] The GLP-1 agonist can be administered at the usual dose and at the usual time although dosing at iftaar (evening) may be preferable. Patients wishing to fast and requiring the addition of a GLP-1 agonist should be initiated on the drug at least four to six weeks prior to Ramadan to allow dose titration and management of side effects (nausea) before they start fasting.

26.6 Insulin therapy

26.6.1 Common regimens

Many patients with type 2 diabetes require insulin to control their diabetes and a variety of insulin regimens are used. These include intermediate or long acting basal insulin only (usually combined with oral agents); premix insulin; and basal-bolus insulin, and these can either be human insulin or analogue insulin or a combination. It must be emphasised that the administration of insulin via the subcutaneous, intramuscular or intravenous route does not break the fast.

While in an ideal setting, overnight intermediate-acting insulin should be injected with a rapid-acting insulin before meals,[22] this is not always easy to implement. Asking patients to change their regimen for Ramadan only may lead to errors, non-adherence and require additional education that is not readily available due to time and resource constraints. The dosing regimen of the insulins used prior to Ramadan may therefore be adjusted to enable safe fasting. If this is unsuccessful then a new regimen may be considered. In addition to modification of the insulin regimens, monitoring of blood glucose levels and self-titration of insulin doses while fasting need to be emphasised to enable safe fasting.

Whilst hypoglycaemia risk may be higher with insulin therapy during Ramadan, there is some evidence that insulin analogues, if used in preference to human insulin, minimises this risk.[23,24] In addition insulin analogues are associated with less post-prandial hyperglycaemia when compared to human insulin.[24] From a practical point, since insulin analogues are injected just before a meal unlike regular insulin; this property is advantageous in that it enables the patient to administer the injection at the time of breaking the fast. It is therefore recommended that patients wishing to fast be switched to insulin analogues for the month of Ramadan if hypoglycaemia, patient convenience and postprandial hyperglycaemia are concerns.[25] The starting dose of analogue insulin should be 20-30% less than the dose of regular insulin.[25]

As with all diabetic therapies the insulin regimen must be individualised according to the patient's needs taking into account their education, preference, diet and lifestyle. If a patient is well controlled prior to Ramadan it is recommended that the total daily dose be decreased by 20-30% at the start of Ramadan and titrated according to the algorithm below (Table II).

The following serves as a guide on how to initiate some of the common insulin regimens.

Table II: Initiation of some common insulin regimens

Basal Insulin	Consider decreasing dose by 20% in well controlled patients.
Once daily dose	Take dose either at Iftaar or bedtime
Twice daily dose	Keep full dose at Iftaar. Half dose at Suhur
Low ratio Premix insulin[24]	
Once daily dose	Same dose given at Iftaar. Titrate doses as per algorithm. If still uncontrolled, change to twice daily premix insulin
Twice daily dose	Prescribe the usual morning dose at Iftaar Half the usual evening dose at Suhur Titrate doses as per algorithm
Thrice daily dose	Omit lunch dose. Adjust other doses as twice daily

Table III: Titration of basal/premix insulin doses (adapted from Hassaneinet al[25])

Fasting/pre-iftaar/pre-suhur BG	Basal/Premix insulin units*
<3.9 mmol/L or symptoms	Break the fast and down titrate by 2 units
4.0-5.0 mmol/L	–2 IU
5.1-7.0 mmol/L	No change
7.1-16.5 mmol/L	+2 IU
> 16.6 mmol/L	Break the fast and check for ketones Increase dose by 4 units

*Pre-iftaar dose to be adjusted based on pre-suhur BG and pre-suhur dose to be adjusted based on pre-iftaar BG levels

26.6.2 Other insulin regimens

If evening post-prandial hyperglycaemia persists despite adequate pre-prandial blood glucose levels, then a premixed insulin in a 50:50 ratio of a rapid acting insulin analogue and a neutral protaminated insulin analogue may be used for the iftaar (evening) meal.[26]

A regimen with pre-suhur (morning) detemir and iftaar (evening) insulin aspart/protamine-crystallised insulin aspart in the ratio 70/30 has also been shown to control glucose levels with a suggestion of less hypoglycaemia.[27] However, this will require a significant change for most patients and may lead to errors if education is inadequate.

When basal bolus insulin is used, the basal dose is adjusted as above. The prandial doses are given prior to Iftaar and suhur (morning). These doses should be decreased by 20-30% as well and then titrated to a two hour post-prandial glucose level < 10mmol/L without hypoglycaemia. The lunch time dose is omitted.

26.6.3 Insulin Titration during Ramadan

It is advisable to titrate the insulin dose every three to four days.[25] The lowest of the three readings on three consecutive days should be used to up titrate the insulin dose.[25]

Hypoglycaemia is defined as blood glucose level below 3.9 mmol/L or symptoms of hypoglycaemia. If hypoglycaemia is noted at any time of the day (even close to Iftaar) in any patient on insulin therapy the fast must be broken and the insulin dose down titrated the following day.[25]

Authors: Hoosen A Randeree, Mohamed AK Omar and Nazeer A Mohamed
Editors: Tanya E Kinvig and Aslam Amod

References

This guideline was adapted from: International Diabetes Federation and the DAR International Alliance. Diabetes and Ramadan: Practical Guidelines. Brussels, Belgium: International Diabetes Federation, 2016. www.idf.org/guidelines/diabetes-in-ramadan and www.daralliance.org. Accessed 22 February 2017.

1. The Quran 2: 183 - 185
2. Ahmed AF, Saleem Y, Abuaisha H. Ramadan fasting and insulin- dependent diabetes: effect in clinical and biochemical control. IntDiab Digest 1993, 4: 88-89
3. Beshyah S.A. Fasting during the month Ramadan for people with diabetes: Medicine and FiqhUnited at last. Ibnosina J Medicine and Biomedical Sciences, 2009 : 1 (2) : 58 - 60
4. The Quran 2: 195
5. Bolen S, Feldman L, Vassy J et al. Systemic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007 ; 147(6) : 386 -99
6. Pan C, Yang W, Barona JP et al. Comparison of vildagliptin and acarbose monotherapy in patients with Type 2 diabetes: a 24 week, double blind, randomized trial. Diabet Med 2008 ; 25(4) : 435 - 41
7. Sari R ,Balci M , Akbar S et al.The effect of diet, sulphonylurea, and repaglinide therapy on clinical and metabolic parameters in type 2 diabetic patients in Ramadan. Endocr Res 2004 ; 30(92) : 169 – 77
8. Anwar A, Azmi KN, Hamidon BB et al. An open label comparative study of glimepiride versus repaglinide in type 2 diabetes mellitus Muslim subjects during the month of Ramadan. Med J Malaysia 2006 ; 61(1) : 28 – 35
9. Vasan S, Thomas N, Bharani et al.A double blind, randomised, multicentre study evaluating the effects of pioglitazone in fasting Muslim subjects during Ramadan. Int J Diabetes Dev C 2006 ; 26 : 70 – 76
10. Mafauzy M. Repaglinide versus glibenclamide treatment of type 2 diabetes during Ramadan fasting. Diabetes Res ClinPract 2002 ; 58(1) : 45 - 53
11. Glimepiride in Ramadan (GLIRA) Study Group. The efficacy and safety of glimepiride in the management of type 2 diabetes in Muslim patients during Ramadan. Diabetes Care 2005 ; 28(2): 421 - 2
12. Zargar A H, Siraj M, Jawa AA, Hasan M, Maktab H. Maintenance of glycaemic control with the evening administration of a long acting sulphonylurea in male type 2 diabetic patients undertaking the Ramadan fast. Int J ClinPract 2010 ; 64 : 1090 – 4
13. Al Sifri, Bassiounny A, Echtay A et al. The incidence of hypoglycaemia in Muslim patients with type 2 diabetes treated with sitagliptin or a sulphonylurea during Ramadan: a randomised trial. IntJClinPract 2011 ; 65 : 1132 – 1140
14. Mbanya JC, Al-Sifri S, Abdel-Rahim A, Satman I. Incidence of hypoglycemia in patients with type 2 diabetes treated with gliclazide versus DPP-4 inhibitors during Ramadan: A meta-analytical approach. Diabetes Res Clin Pract. 2015;109(2):226-232. doi:10.1016/j.diabres.2015.04.030.
15. H HLoh et al Prim.CareDiab 2015http://dx.doi.Org/10.1016/j.pcd.2015.09.001
16. Devandra D, Gokel B, Bravis V et al. Vildagliptin therapy and hypoglycaemia in Muslim type 2 diabetes patients during Ramadan. Int J ClinPract 2009 ; 63 : 1446 -1450
17. Hassanein M, Abdallah K, Schweizer A et al. A double – blind , randomised trial , including frequent patient – physician contacts and Ramadan – focussed advice, assessing vildagliptin and gliclazide in patients with Type 2 diabetes fasting during Ramadan: the STEADFAST study. Vasc Health Risk Manag 2014 ; 10 : 319 - 26
18. Hassanein M, Hanif W, Malik W et al. Comparison of the dipeptidyl peptidase – 4 inhibitor vildagliptin and the sulphonylurea gliclazide in combination with metformin in Muslim patients with type 2 diabetes mellitus fasting during Ramadan: results of the VECTOR study. Current Med Res Opin 2011 ; 27 : 1367 - 74
19. Brady E, Davies M, Gray L, Saeed M, Smith D, Hanif W et al. A randomized controlled trial comparing the GLP-1 receptor agonist liraglutide to a sulphonylurea as add on to metformin in patients with established type 2 diabetes during Ramadan: the Treat 4 Ramadan Trial. Diabetes ObesMetab. 2014;16(6):527-536.
20. Azar ST, Echtay A, Wan Bebakar WM, Al Araj S, Berrah A, Omar M et al. Efficacy and safety of liraglutide compared to sulphonylurea during Ramadan in patients with type 2 diabetes (LIRA-Ramadan): a randomized trial. Diabetes ObesMetab. 2016;18(10):1025-1033.
21. Khalifa A, Alaaeldin MK A. Safety and Efficacy of Liraglutide as an Add-On Therapy to Pre-Existing Anti-Diabetic Regimens during Ramadan, A Prospective Observational Trial. Journal of Diabetes & Metabolism. 2015;06(09).
22. Al-Arouj M, Assaad-Khalil S, Buse J, Fahdil I, Fahmy M, Hafez S et al. Recommendations for Management of Diabetes During Ramadan: Update 2010. Diabetes Care. 2010;33(8):1895-1902.

23. Mattoo V, Milicevic Z, Malone J, Schwarzenhofer M, Ekangaki A, Levitt L et al. A comparison of insulin lispro Mix25™ and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. Diabetes Research and Clinical Practice. 2003;59(2):137-143.
24. Akram J, De Verga V, Group t. Insulin lispro (Lys(B28), Pro(B29)) in the treatment of diabetes during the fasting month of Ramadan. Diabetic Medicine. 1999;16(10):867-874.
25. Hassanein M, Belhadj M, Abdallah K, Bhattacharya A, Singh A, Tayeb K et al. Management of Type 2 diabetes in Ramadan: Low-ratio premix insulin working group practical advice. Indian Journal of Endocrinology and Metabolism. 2014;18(6):794.
26. Hui E, Bravis V, Salih S, Hassanein M, Devendra D. Comparison of Humalog Mix 50 with human insulin Mix 30 in type 2 diabetes patients during Ramadan. International Journal of Clinical Practice.2010;64(8):1095-1099.
27. Shehadeh N, Maor Y. Effect of a new insulin treatment regimen on glycaemic control and quality of life of Muslim patients with type 2 diabetes mellitus during Ramadan fast - an open label, controlled, multicentre, cluster randomised study. International Journal of Clinical Practice. 2015;69(11):1281-1288.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 27: Prevention or delay of type 2 diabetes mellitus

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
All persons with multiple risk factors for diabetes should be offered structured education regarding diabetes prevention, and be offered a screening test for type 2 diabetes (Chapter 3).	A
Offer intensive interventions supporting lifestyle changes to prevent/delay the onset of T2DM in high-risk adults (those with IFG/IGT). These interventions are cost-effective and should be supported by public health policies and 3rd party payers.	A
Offer intensive lifestyle interventions as part of a structured programme that is based on proven principles. Use this to support the individual with IGT/IFG to: 1. Achieve and maintain weight loss >5% 2. Modify dietary patterns focusing on a. Reducing energy from fat to ≤30% b. Reducing energy from saturated fat to ≤10% c. Increasing fiber intake ≥15 g/1,000 kcal 3. Increase moderate intensity physical activity ≥ 150 minutes per week Frequent contact and follow-up improves intervention success.	A
Consider metformin for individuals who have deteriorating FPG or 2-h PG after 6 months, and: 1. Have participated in an intensive lifestyle intervention programme, or 2. Have been unable to participate in an intensive lifestyle intervention programme. Especially those who: a. Are less than 60 years old b. Have a history of gestational diabetes c. Have a BMI > 35 kg/m^2 d. Have combined IFG and IGT e. Have the metabolic syndrome Continue to support the individual with intensive lifestyle interventions.	A
Monitor IFG/IGT every 6-12 months and intensify lifestyle interventions and the metformin dose if blood glucose does not improve. If metformin is ineffective consider an alternative drug (acarbose or orlistat).	B
Persons with IFG/IGT must be screened for other cardiovascular risk factors, including metabolic syndrome (Chapter 16). These risk factors must be managed optimally.	A

27.1 Introduction

Diabetes is a worldwide pandemic associated with significant morbidity and mortality. The global incidence of diabetes is projected to increase to 642 million by 2040.[1] Early detection of those at risk for the development of diabetes and early intervention strategies can prevent the progression to diabetes and its associated microvascular and macrovascular complications. This chapter focuses on diabetes prevention in easily defined groups at high risk for progression to type 2 diabetes i.e those with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), as prospective randomised prevention trials have focused almost exclusively on this group.

27.2 Identifying individuals at increased risk

The risk factors for the development of diabetes are listed in Chapter 3 and duplicated here for convenience (Table I). Multiple scoring systems exist for predicting risk and to identify indvividuals for diabetes screening; however these tend to be ethnic specific and not universally applicable.[2] There is no risk scoring system available for South Africa. IFG and IGT are categories of intermediate hyperglycaemia which easily

and clearly define individuals and populations at high risk for progression to diabetes and cardiovascular disease (CVD), and therefore represent a group that can and have been targeted for prevention strategies. This does not imply that individuals without IFG or IGT, who have other risk factors listed in Table I are not at risk, and they should also be targeted with lifestyle interventions for prevention. The ideal method of identifying people at highest risk for diabetes and CVD would be a risk assessment tool which uses all the risk factors in Table I and includes plasma glucose as a continuous variable rather than a categorical one; this has not been developed yet.

Table I: Risk factors for type 2 diabetes[3]

Age >45 years
All adults at any age who are overweight (BMI> 25 kg/m^2 or > 23 kg/m^2 in Asians), plus one or more additional risk factors: • Previous IFG or IGT • Physical inactivity • High-risk race/ethnicity (Asian and Coloured) • First degree relative with diabetes • History of cardiovascular disease • Hypertension [Blood pressure (BP) ≥ 140/90 mmHg] or treatment for hypertension • Dyslipidaemia (low HDL and/or high triglycerides) • Polycystic ovarian syndrome • History of gestational diabetes or having delivered a baby > 4 kg • Other conditions associated with insulin resistance (e.g. severe obesity, acanthosis nigricans)

An OGTT is preferred in high risk individuals as it is a more sensitive test, and is the only method to diagnose IGTwhich is a strong risk factor for CVD.

27.2.1 Defining categories of increased risk for diabetes

The diagnosis of IFG and IGT have been discussed in Chapter 3. In summary plasma glucose as a risk factor for future diabetes is a continuous variable, meaning that the higher the plasma glucose, even in the so-called normal range, the higher is the risk for future diabetes. The cut-points that define IFG (6.1 to 6.9 mmol/L) and IGT (2-h PG 7.8 to 11.0 mmol/L) are arbitrary cut-points that define higher risk based on, inter-alia, the feasability of public health interventions. In this regard the ADA has chosen to define IFG using a lower cut-point (FPG 5.6 to 6.9 mmol/L) for intervention. The ADA has also chosen to include HbA$_{1c}$ values in the abnormal but non-diabetic range (5.7 to 6.4%) in the category of prediabetes, together with IFG and IGT. SEMDSA has aligned itself with the WHO position which is to retain the FPG cutpoint of 6.0 mmol/L for IFG and to not include HbA$_{1c}$ to define intermediate hyperglycaemia. Rather, a FPG or 2-h PG measurement is recommended for individuals with HbA$_{1c}$ 5.7 to 6.4% when intervention is planned. The term prediabetes, when used, will refer to the two categories of intermediate hyperglycaemia viz. IFG and IGT. The measurement of insulin levels plays no role in the assessment of prediabetes in clinical practice.

27.2.2 Epidemiology of risk

According to an ADA expert panel the lifetime risk of people with IFG or IGT developing diabetes was 70%.[2] A meta-analysis of prospective studies showed that the annual incidence of diabetes in individuals with isolated IFG or IGT was 6-9% and 4-6% per year respectively. The incidence in persons with both IFG and IGT was significantly higher (15-19%/yr).[4] Another meta-analysis of prospective studies reported that the rates of progression to diabetes (no. per 1000 person-years) for the categories HbA$_{1c}$ 6.0-6.4%, ADA defined-IFG, WHO defined-IFG, IGT and combined IFG+IGT was 35.6, 35.5, 47.4, 45.5 and 70.4 respectively.

In South African Indians with IGT, the annual incidence of diabetes was found to be 12.6% per year over four years.[5] Women with a history of gestational diabetes also have a particularly high risk of progressing to diabetes (20-60% over the 5 to 10 years after the pregnancy).[2] The South African National Health and Nutrition Examinations Survey (SANHANES) in 2012 determined that the national prevalence of HbA$_{1c}$ values between 6.0 to 6.4% is 8.9% for the population older than 15 years, representing about 5 million individuals at risk for diabetes. In this regard it is noteworthy that HbA$_{1c}$ in this range identifies a much smaller population with prediabetes than do IFG and IGT.[6]

IFG and IGT are also risk factors for CVD. A meta-analysis of 53 prospective cohort studies with 1 611 339 individuals followed over 9 years reported that the relative risk (RR) for composite cardiovascular endpoints was ~1.3 for either IFG or IGT. All cause mortality was significantly higher for IGT compared to IFG.[7] The metabolic syndrome (Chapter 16) is an independent risk factor for CVD (RR 2.0) so it follows that individuals with IFG/IGT with the metabolic syndrome are equally at high risk.[8,9]

27.3 Clinical trials for the prevention of type 2 diabetes

A number of well-designed intervention studies using lifestyle (diet and exercise) or drug therapy have been conducted. Trials that implemented **lifestyle modification only** such as the Finnish Diabetes Prevention Study (DPS) and the Chinese Da Qing Study have both conclusively shown that the development of type 2 diabetes in people with pre-diabetes can be prevented by making changes in the diet to promote moderate weight loss, and by increasing their level of physical activity.[10,11]

The Finnish DPS established a precedent for effectively altering lifestyle in patients with a high risk for diabetes. It studied 522 subjects with IGT using the 1999 WHO criteria (FPG < 7.8 mmol/l; 2 hrs post glucose load 7.8-11.1 mmol/l). The intensive lifestyle modification group showed a 58% relative risk reduction in the progression to diabetes as compared to controls, and continued effects were seen as a result of lifestyle change.[10]

In the **Da Qing** study, 577 Chinese subjects with IGT were randomised for 6 years either to a control group, dietary intervention, exercise, or a combination of diet and exercise, and followed over 6 years. Compared with control participants, those in the combined lifestyle intervention groups had a 51% lower incidence of diabetes (HR 0.49; 95% CI 0.33-0.73) during the active intervention period and a 43% lower incidence (HR 0.57; 0.41-0.81) over a 20 year period.[11,12] After 23 years of follow-up they were able to show that mortality in this group with IGT was related to progression to diabetes; delaying the diagnosis of diabetes was associated with lower mortality.[13] Thus, a 6-year lifestyle intervention showed the long-term clinical benefits for patients with IGT and provides further justification for adoption of lifestyle interventions.

Other trials have implemented **pharmacological interventions** and/or lifestyle interventions to delay or prevent the onset of diabetes and these include, the U.S-based Diabetes Prevention Program (DPP),[14] the Troglitazone in Prevention of Diabetes Trial (TRIPOD),[15–18] Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial,[19] the STOP-NIDDM Trial,[20] the Indian Diabetes Prevention Programme (Indian DPP),[21] and the Actos Now for Prevention of Diabetes (ACT Now) trial.[22]

The **US-DPP** investigated the efficacy of intensive, behavioural lifestyle modification using individualised and group therapy to achieve and maintain >7% body weight loss and physical activity equivalent to at least 150 min/week of moderate intensity exercise.[1-4,15] After 2.8 years, lifestyle intervention decreased the incidence of type 2 diabetes by 58% compared with 31% in the metformin-treated group. The DPP Outcomes Study (DPPOS) followed up surviving participants from the DPP; the original lifestyle intervention group was offered lifestyle reinforcement semi-annually and the metformin group received unmasked metformin. During a mean follow-up of 15 years, diabetes incidence was reduced by 27% in the lifestyle intervention group (<0·0001) and by 18% in the metformin group (p=0·001), compared with the placebo group. At year 15, the cumulative incidences of diabetes were 55% in the lifestyle group, 56% in the metformin group, and 62% in the placebo group. Lifestyle intervention or metformin significantly reduced diabetes development over 15 years and supports the strategy of diabetes prevention.[23]

Table II: Summary of trials for prevention of Type 2 diabetes

STUDY, n, type	THERAPY	RELATIVE RISK REDUCTION
Finnish Diabetes Prevention Study (FDPS), n=522, RCT	Diet + Exercise	58%
Da Qing Study, n=577, RCT	Diet Exercise Diet + Exercise	31% 46% 42% (51%)
US-Diabetes Prevention Program (DPP) n= 1079, RCT	Diet + Exercise Metformin 850mg bd	58% 31%
Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM), n=5269, RCT	Rosiglitazone + Diet + Exercise + Ramipril	60%
Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP- NIDDM) trial, n=1418, RCT	Acarbose	25%
Actos now (ACT NOW) for prevention of Diabetes Study, n=602, RCT	Pioglitazone	81%
Indian DPP, n=531, RCT	Diet + Exercise Metformin 250mg bd Diet, Exercise + Metformin 250mg bd	28.5% 26.4% 28.2%

The **Indian DPP** study reported a 28.5% relative risk reduction in progression to diabetes with lifestyle intervention and a 26.4% reduction with metformin 250 mg twice daily versus controls. This dose of metformin when added to lifestyle modification, yielded no further benefit for progression to diabetes.[21]

The **TRIPOD** (TRoglitazone In the Prevention Of Diabetes) study in Hispanic women with GDM showed a reduction of 55% after 30 months, which was maintained at 8 months following discontinuation of the drug.

The **STOP-NIDDM** (Study To Prevent Non-Insulin Dependent Diabetes Mellitus) showed a 25% relative reduction of developing diabetes in those treated with acarbose versus placebo after 3.3 years. The trial also showed that targeting postprandial hyperglycaemia with acarbose was associated with a 49% relative risk reduction in the development of cardiovascular events.[24] Acarbose was also associated with a 34% relative risk reduction in the incidence of new cases of hypertension.[24] However 31% of patients in the acarbose arm withdrew due to side-effects and the number of CV events was low.[20] placebo-controlled randomised trial, we randomly allocated patients with impaired glucose tolerance to 100 mg acarbose or placebo three times daily. The primary endpoint was development of diabetes on the basis of a yearly oral glucose tolerance test (OGTT Nevertheless the results remain significant.

The **XENDOS** (XENical in the prevention of Diabetes in Obese Subjects) showed a relative reduction of 37.3% in those treated with orlistat and lifestyle modification versus placebo; the best reduction was noted in the IGT group where the incidence of diabetes was reduced by 45% over 4 years.[25]

The **DREAM** (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) showed a reduction of 60% in those treated with rosiglitazone (but an increase in oedema and heart failure) versus ramipril and placebo after 3 years.[19]

The **ACT NOW** (Actos Now for the prevention of diabetes) study showed a reduction in the risk of conversion to diabetes of 72% versus placebo over 2.4 years.[22] More recently, in a study of people without diabetes but with insulin resistance and cerebrovascular disease, pioglitazone halved the progression to type 2 diabetes. Concerns with the side effects of pioglitazone (more oedema, weight gain and higher fracture rate) compared to placebo still remain.[22,26]

27.4 The role of lifestyle modification in diabetes prevention / delay

Interventions supporting lifestyle changes delay the onset of T2DM in high-risk adults and are very effective; the number-needed-to-treat to prevent one new case of diabetes is 6.4 over 1.8–4.6 years.[27] The DPP lifestyle intervention has been criticised for being too intensive and expensive yet cost analyses show it to be very cost-effective.[28] In fact translational research examining the implmentation of lifestyle intervention programmes in the "real-world" setting, using less intensive approaches and scaleable models for intervention such as group interventions have consistently demonstrated their effeciveness and cost-effectiveness.[29,30]

The key components of *effective and successful* lifestyle intervention programmes for the prevention of diabetes have included:

1. Weight manangement in overweight and obese individuals with the aim of achieving and maintaining a >5% weight loss by reducing caloric intake. Lesser degrees of weight loss are still beneficial. Data from the U.S. DPP study showed that each kilogram of mean weight loss is associated with a reduction of ~16% in future diabetes incidence. Real-world data showed mean weight loss of -2.6% over 12 months was beneficial.[29]
2. Key dietary changes which are beneficial independent of weight loss:
    a. Reduce energy from fat to ≤30%
    b. Reduce energy from saturated fat to ≤10%
    c. Increased fiber intake ≥15 g/1,000 kcal
3. Increase moderate intensity physical activity (e.g. brisk walking) to ≥30 min/day or 150 minutes per week

Success of a lifestyle intervention programme is directly related to degree to which the programme is structured and adheres to the suggested dietary and exercise guidlines, programme intensity (frequency of contact), and the degree of uptake by the community.[29,30] However, even low intesity programmes that lead to only moderate weight loss can still have a considerable impact in lowering diabetes risk in a population. From a public health perspective, this is an important finding, especially for resource constrained settings.[31]

The strategies for supporting successful behaviour change and the healthy behaviours recommended for people with prediabetes are largely identical to those for people with diabetes. Given their training and experience, providers of DSME and DSMS are particularly well equipped to assist people with prediabetes in developing and maintaining behaviours that can prevent or delay the onset of diabetes. Evidence from studies in low/middle income countries show that structured lifestyle education programmes delivered by allied health professionals (e.g. nurses, pharmacists) can be as effective as those led by clinicians.[31] In addition, group delivery of intensive lifestyle intervention content in community settings can reduce overall programme costs while still producing weight loss and diabetes risk reduction.[32]

27.5 The role of pharmacological therapy in diabetes prevention / delay

The exact role of drug therapy in the prevention of diabetes remains unclear. Controversial issues include the duration of drug therapy and whether drugs alter or reverse the underlying disease process and actually prevent progression to diabetes, as opposed to delaying or masking it. Data from the studies above indicate that benefit from glucose lowering drugs is lost when the treatment is stopped, implying that treatment may need to be taken indefinitely. The ideal drug for diabetes prevention should be safe, effective, inexpensive, demonstrate reversal of the underlying pathophysiologic process and improve clinical outcomes such as cardiovascular morbidity and mortality.[33] Since none of the drugs studied thus far can fulfil these criteria, the mainstay of therapy still remains intensive lifestyle intervention with diet and exercise. Based on the available trials, four (4) of the pharmacologic agents can be considered for the prevention of type 2 diabetes. These include metformin, acarbose, orlistat and pioglitazone. Pioglitazone is available as a generic and is relatively inexpensive. However side-effects such as weight gain and oedema and its cumulative effect over time on long-bone fractures limit its use (patients will need to take the drug for many years). Acarbose was very effective and reduced CV events, but the dropout rate in the STOP-NIDDM trial was very high because of the drugs poor GI tolerability. There is also no generic formulation and the drug remains expensive. Orlistat has the same limitations as acarbose i.e side-effects and cost.

Metformin has strong evidence to support its use, has a long, proven safety profile, is well tolerated and is also the least expensive drug option. The evidence from the US-DPP showed clearly that intensive lifestyle modification was superior to metformin in preventing and delaying the progression to diabetes. Also, in the US-DPP there were identifiable subgroups with differential responses to metformin:

- Persons older than 60 years did not benefit from metformin.
- Persons with a BMI ≥ 35 kg/m^2 had a better response than those with a lower BMI.
- In women with a history of gestational diabetes, metformin was as effective as intensive lifestyle intervention (50% reduction in progression).[34]

In the Indian-DPP metformin 250 mg BD was as effective as lifestyle modification, which was less intensive than in the US-DPP.

27.6 Recommendations

All persons with mutiple risk factors for type 2 diabetes should receive education about lifestyle modification to prevent diabetes. Persons with IFG and/or IGT are at high risk for progression to diabetes and CVD, and should be offered structured intensive lifestyle interventions programmes with the aim of >5% weight loss, dietary modifications and at least moderate intensity exercise for >150 minutes per week. IFG/ IGT should be reassesed every 6-12 months and if the trajectory towards diabetes does not reverse then pharmacological therapy should be considered.

Pharmacological intervention should be considered for subgroups a) who have a very high risk of progression to diabetes, or b) are known to derive particular benefit with metformin therapy.

Metformin standard-release should therefore be considered for individuals who have deteriorating FPG or 2-h PG who:

a. Have been participating in an intensive lifestyle intervention programme, *or*
b. Have not been able to participate in an intensive lifestyle intervention programme,

Especially if he/she:

1. Is < 60 years old
2. Has a history of gestational diabetes
3. Has a BMI > 35 kg/m^2
4. Has both IFG and IGT
5. Has the metabolic syndrome

The dose of standard-release metformin employed in the Indian DPP was 500 mg daily while the US-based DPP used 1700 mg daily, both in divided doses.[14,21] The individual will need to be counselled that the drug is being used "off-label". Acarbose and orlistat are alternatives to using metformin but are more expensive. Follow the manufacturers directions for use.

Monitor the FPG and/or 2-h PG every 3 to 6 months and increase the dose if these are deteriorating. Stop therapy if there is no response and consider alternative therapies (acarbose, orlistat).

27.7 The management of obesity for the prevention of prediabetes

Retrospective data analysis from bariatric surgery trials have shown a significant reduction in the prevalence of type 2 diabetes and pre-diabetes among morbidly obese patients who have undergone bariatric surgery. However, in view of its costs, related morbidity and other long term effects, it cannot be recommended for the management of prediabetes alone.[35] High doses of liraglutide have also demonstrated reduction of the rates of prediabetes in a weight loss trial of obese subjects.[36] There are no published diabetes prevention trials with GLP-1 agonists compared to lifestyle intervention. The role of obesity in type 2 diabetes is discussed in Chapter 15.

Authors: Pankaj Joshi and Aslam Amod
Editor: Imran Paruk

References

1. International Diabetes Federation. IDF Diabetes Atlas, 7 ed. Int Diabetes Fed. 2015. http://www.idf.org/diabetesatlas. Accessed January 2, 2016.
2. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379(9833):2279-2290. doi:10.1016/S0140-6736(12)60283-9.
3. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care. 2017;40(Supplement 1):S11-S24. doi:10.2337/dc17-S005.
4. Gerstein HC, Santaguida P, Raina P, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: A systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract. 2007;78(3):305-312. doi:10.1016/j.diabres.2007.05.004.
5. Motala AA, Omar MAK, Gouws E. High Risk of Progression to NIDDM in South-African Indians with Impaired Glucose Tolerance. Diabetes. 1993;42(4):556-563. doi:10.2337/diab.42.4.556.
6. Buysschaert M, Medina J-L, Buysschaert B, Bergman M. Definitions (and Current Controversies) of Diabetes and Prediabetes. Curr Diabetes Rev. 2015;12(1):8-13. doi:10.2174/1573399811666150122150233.
7. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ. 2016;355:i5953. doi:10.1136/bmj.i5953.
8. Gami AS, Witt BJ, Howard DE, et al. Metabolic Syndrome and Risk of Incident Cardiovascular Events and Death. J Am Coll Cardiol. 2007;49(4):403-414. doi:10.1016/j.jacc.2006.09.032.
9. Mottillo S, Filion KB, Genest J, et al. The Metabolic Syndrome and Cardiovascular Risk. J Am Coll Cardiol. 2010;56(14):1113-1132. doi:10.1016/j.jacc.2010.05.034.
10. Tuomilehto J, Lindström J, Eriksson JG, et al. Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance. N Engl J Med. 2001;344(18):1343-1350. doi:10.1056/NEJM200105033441801.
11. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997;20(4):537-544.
12. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet. 2008;371(9626):1783-1789. doi:10.1016/S0140-6736(08)60766-7.
13. Li G, Zhang P, Wang J, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol. 2014;2(6):474-480. doi:10.1016/S2213-8587(14)70057-9.
14. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA NDDPPRG. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. N Engl J Med. 2002;346(6):393-403. doi:10.1056/NEJMoa012512.
15. Alberti KGMM. Screening and diagnosis of prediabetes: where are we headed? Diabetes, Obes Metab. 2007;9(s1):12-16. doi:10.1111/j.1463-1326.2007.00764.x.
16. Standards of Medical Care in Diabetes--2011. Diabetes Care. 2011;34(Supplement_1):S11-S61. doi:10.2337/dc11-S011.
17. Fonseca VA. Identification and treatment of prediabetes to prevent progression to type 2 diabetes. Clin Cornerstone. 2007;8(2):10-8-20.
18. Aroda VR, Ratner R. Approach to the Patient with Prediabetes. J Clin Endocrinol Metab. 2008;93(9):3259-3265. doi:10.1210/jc.2008-1091.
19. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet (London, England). 2006;368(9541):1096-1105. doi:10.1016/S0140-6736(06)69420-8.
20. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet. 2002;359(9323):2072-2077. doi:10.1016/S0140-6736(02)08905-5.
21. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49(2):289-297. doi:10.1007/s00125-005-0097-z.
22. DeFronzo RA, Tripathy D, Schwenke DC, et al. Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance. N Engl J Med. 2011;364(12):1104-1115. doi:10.1056/NEJMoa1010949.
23. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol. 2015;3(11):866-875. doi:10.1016/S2213-8587(15)00291-0.
24. Chiasson J-L, Josse RG, Gomis R, et al. Acarbose Treatment and the Risk of Cardiovascular Disease and Hypertension in Patients With Impaired Glucose Tolerance. JAMA. 2003;290(4):486. doi:10.1001/jama.290.4.486.
25. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004;27(1):155-161.
26. Inzucchi SE, Viscoli CM, Young LH, et al. Pioglitazone Prevents Diabetes in Patients With Insulin Resistance and Cerebrovascular Disease. Diabetes Care. 2016;39(10):1684-1692. doi:10.2337/dc16-0798.
27. Paulweber B, Valensi P, Lindström J, et al. A European Evidence-Based Guideline for the Prevention of Type 2 Diabetes. Horm Metab Res. 2010;42(S 01):S3-S36. doi:10.1055/s-0029-1240928.

28. The 10-Year Cost-Effectiveness of Lifestyle Intervention or Metformin for Diabetes Prevention: An intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care*. 2012;35(4):723-730. doi:10.2337/dc11-1468.

29. Dunkley AJ, Bodicoat DH, Greaves CJ, et al. Diabetes Prevention in the Real World: Effectiveness of Pragmatic Lifestyle Interventions for the Prevention of Type 2 Diabetes and of the Impact of Adherence to Guideline Recommendations. *Diabetes Care*. 2014;37(4):922-933. doi:10.2337/dc13-2195.

30. Aziz Z, Absetz P, Oldroyd J, Pronk NP, Oldenburg B. A systematic review of real-world diabetes prevention programs: learnings from the last 15 years. *Implement Sci*. 2015;10(1):172. doi:10.1186/s13012-015-0354-6.

31. Afable A, Karingula NS. Evidence based review of type 2 diabetes prevention and management in low and middle income countries. *World J Diabetes*. 2016;7(10):209-229. doi:10.4239/wjd.v7.i10.209.

32. 5. Prevention or Delay of Type 2 Diabetes. *Diabetes Care*. 2017;40(Supplement 1):S44-S47. doi:10.2337/dc17-S008.

33. Pour OR, Dagogo-Jack S. Prediabetes as a Therapeutic Target. *Clin Chem*. 2011;57(2):215-220. doi:10.1373/clinchem.2010.149096.

34. Ratner RE, Christophi CA, Metzger BE, et al. Prevention of Diabetes in Women with a History of Gestational Diabetes: Effects of Metformin and Lifestyle Interventions. *J Clin Endocrinol Metab*. 2008;93(12):4774-4779. doi:10.1210/jc.2008-0772.

35. de la Cruz-Muñoz N, Messiah SE, Arheart KL, Lopez-Mitnik G, Lipshultz SE, Livingstone A. Bariatric Surgery Significantly Decreases the Prevalence of Type 2 Diabetes Mellitus and Pre-Diabetes among Morbidly Obese Multiethnic Adults: Long-Term Results. *J Am Coll Surg*. 2011;212(4):505-511. doi:10.1016/j.jamcollsurg.2010.12.015.

36. Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med*. 2015;373(1):11-22. doi:10.1056/NEJMoa1411892.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 28: Diabetes and driving

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Patients must be educated that diabetes can affect driving performance because of chronic complications that impair sensory or motor functions and because of transient cognitive dysfunction resulting from medication-induced hypoglycaemia.	C
Fitness to drive should be assessed on a case-by-case basis by the treating physician, and should not solely be based on a diagnosis of diabetes.	C
Patients must be educated about risks associated with driving as well as appropriate precautions when driving as part of structured diabetes education.	C
Since the most significant factor associated with driving collisions appears to be a recent history of hypoglycaemia, drivers who experience a severe hypoglycaemic event (defined as an event requiring outside help, or resulting in loss of consciousness or seizure while driving) should ideally not drive until cleared by an appropriate medical practitioner.	C
If a severe hypoglycaemic event occurs, the person should not drive for a minimum period of six weeks thereafter, and only once hypoglycaemic awareness is re-established.	C
Health-care professionals should be aware of the medical standards for fitness to hold a driver's licence.	C
People using insulin and/or insulin secretagogues must be counselled about the precautions to take for hypoglycaemia.	C
People with diabetes who are medically unfit to drive should be informed of their legal obligation, under the National Road Traffic Act, 93 of 1996, to inform the local Licensing Department of such. A family member of the patient should also be advised of this obligation.	C
Consider using glucose-lowering drugs with the lowest risk of hypoglycaemia in people who operate public transport and heavy-duty vehicles.	C
Visual acuity must be tested annually.	A

28.1 Introduction

For many South Africans, driving is an essential part of daily living and is often a requirement of employment. Diabetes can affect driving performance because of chronic complications that impair sensory or motor functions (retinopathy, neuropathy, amputation, vascular disease) and because of transient cognitive dysfunction or loss of consciousness resulting from medication-induced hypoglycaemia. The presence and extent of these factors vary from person to person, so the fitness of persons with diabetes to drive should be assessed on an individual basis. There has been considerable debate whether, and the extent to which, diabetes may be a relevant factor in determining driver ability and eligibility for a driver's license. The current evidence has recently been reviewed in detail in position statements from the American and Canadian Diabetes Associations.[1,2]

28.2 Effects of diabetes on ability to drive

Diabetes impacts driving performance particularly when medication results in hypoglycaemia. There is less evidence that hyperglycaemia has major effects on driving. Furthermore, the chronic complications of diabetes such as retinopathy, cataracts and stroke may affect driving performance, as may associated conditions such as sleep apnoea.

Hypoglycaemia may result in transient cognitive dysfunction or loss of consciousness which could impair driving ability. Experimental laboratory studies and studies using a simulator have demonstrated that cognitive functions critical to driving (such as attention, reaction times and hand-eye coordination) are impaired during hypoglycaemia with driving performance adversely affected resulting in inappropriate speeding or braking, ignoring road signs and traffic lights and not keeping to traffic lanes.[3,4]

28.2.1 Diabetes and the risk of road traffic accidents

Overall, studies are inconsistent and there is no strong, epidemiological data that suggest an increase in traffic accidents among people with diabetes. A meta-analysis of 15 studies suggested that the relative risk of having a motor vehicle accident for people with diabetes i.e., without differentiating those with a significant risk from those with little or no risk, as compared

with the general population ranges between 1.12 and 1.19, a 12–19% increased risk.[5] Society tolerates much higher relative risks associated with a variety of other situations such as those with sleep apnoea, the very young driver, and drivers with attention deficit/hyperactivity disorder. It would thus be unjustified to restrict driving privileges of an entire class of individuals, such as drivers with diabetes.

Drivers managing their diabetes with insulin are the most significant subgroup of persons with diabetes, for whom a greater degree of restrictions is often applied across the rest of the world. Yet, when diabetes is controlled, insulin therapy per se has not been found to be associated with increased driving risk. The single most significant factor associated with driving collisions appears to be a recent history of hypoglycaemia.[6,7]

28.3 Current legislation in South Africa

28.3.1 Road user

All drivers who travel on public roads are subject to the requirements of the National Road Traffic Act, 93 of 1996 (RTA) in terms of ensuring their fitness to drive any vehicle (Sections 15 and 16), and in the event of an incident, to the consequences in terms of the offences and penalties contained in the Act. The current legislation in the RTA on Fitness to Drive states that a person shall be disqualified from obtaining or holding a learner's and driver's license "if he or she is suffering from uncontrolled diabetes mellitus." This is, however, not defined further, nor is any mention made of the risks of therapy. Additionally, "sudden attacks of disabling giddiness or fainting" and "defective vision" could be relevant exclusion conditions for a patient with diabetes.

The Act currently puts the burden of proof on the individual, either during the application process or who should "within a period of 21 days after having so become aware of the disqualification submit the license to the MEC of the Province." There is currently no legal requirement for a health care worker to report patients deemed unfit to drive.

Unlike in many other countries in Europe and America, there is currently no separate legislation for drivers of commercial vehicles. Since commercial vehicle drivers drive for longer periods, at faster speeds, and on the highways more than average private drivers, and since commercial vehicles are larger and more lethal than private motor vehicles, or may be involved in public transportation, e.g. buses and mini-bus taxis, the potential for severe and disastrous traffic accidents is clearly of additional concern.

28.3.2 Employer Role

In South African Occupational Health and Safety Legislation there is a dual employee and employer responsibility. The Labour Relations and Employment Equity Acts guide stakeholders and decision makers in a fair and legal framework of "fitness to drive". The employer is, in terms of the RTA, required to categorise all drivers according to the relative risks involved specific to their industry and according to the requirements for the issuing of the Professional Driving Permit. The employer must ensure that drivers undergo the necessary health evaluations as and when required. This must take place at the employer's expense. The employer must provide the examining health professional with the necessary information on the driver's category, special skills required and any known risk factors.

28.4 Recommendations for the South African situation

28.4.1 General

The fitness to drive should be assessed on a case-by-case basis by the treating physician, and should not solely be based on a diagnosis of diabetes, but rather on unequivocal evidence of actual risk (Figure I). Health care professionals should be knowledgeable and regularly discuss ways to reduce the risks of driving with their diabetic patients. Persons with diabetes should take an active role in assessing their ability to drive and in obtaining information about recognition, treatment and avoidance of hypoglycaemia. Healthcare funders should recognise the recommendations for blood glucose monitoring in persons with diabetes who drive and provide adequate blood glucose test strips to cover additional testing before and during driving.

28.4.2 Private vehicles

Persons with diabetes should have no restrictions to drive personal vehicles in general, irrespective of treatment regimen or diabetes type, but ideally require regular medical supervision and assessment (minimum two clinic visits per year). Physicians should look out for the high-risk patient and offer targeted education and advice. Patients who have experienced severe

Figure I: Medical standards for licensing[1,2]

- There is no recent history (generally at least 6 weeks) of a "severe hypoglycaemic event" (requiring assistance from another person).
- The driver experiences early warning symptoms (awareness) of hypoglycaemia.
- The driver must demonstrate an understanding of the risks of hypoglycaemia and is following a treatment regimen that minimises the risk of hypoglycaemia.
- There are no other potentially dangerous complications or comorbidities associated with diabetes, such as:
  - Sight threatening retinopathy or cataracts (a complete eye examination by ophthalmologist or optometrist is mandatory)
  - Obstructive sleep apnoea
  - Unstable coronary artery disease or arrhythmias
  - Transient ischaemic attacks
  - Significant neurological deficits (e.g. cerebrovascular disease, peripheral or autonomic neuropathy).

Figure II: Precautionary steps for drivers regarding hypoglycaemia

- Always carry your glucose meter and blood glucose strips with you.
- Ensure that you have a glucose containing snack that is easily accessible in your vehicle.
- Check your blood glucose no more than one hour before the start of the journey and every two hours during the journey, as reasonably practical.
- Do not drive if blood glucose is at or less than 5 mmol/L.
- Do not drive for more than two hours without considering having a snack. Do not drink alcohol before or while driving.
- Do not delay or miss a main meal.
- Carry adequate glucose in the vehicle for self-treatment.
- If experiencing hypoglycaemia, pull to the side of the road, turn off the engine and remove the keys from the ignition if safe to do so.
- Check the blood glucose levels 15 minutes or more after the hypoglycaemia has been treated and ensuring it is above 5 mmol/L.
- Do not drive until feeling well and until at least 30 minutes after the blood glucose is above 5 mmol/L.
- Carry personal identification to indicate you have diabetes.

hypoglycaemic events or hypoglycaemic unawareness should consult with their health care providers to determine whether it is safe to drive and to implement interventions to avoid further episodes.

28.4.3 Commercial vehicles

Although South African law does not offer specific guidance, it would seem reasonable for physicians to give strong advice here. There should be clear guidance for conducting the annual assessment and specific criteria for holding a commercial license.

Candidates with diabetes who apply for commercial licenses should have an initial full medical assessment, as well as annual reassessment by a specialist physician, endocrinologist or family physician trained in diabetes management, including review of medical records and glucometer recordings of the previous 24 months.

In the interest of patient and public safety, it may be wise to consider using glucose-lowering drugs with the lowest risk of hypoglycaemia in people who operate public transport and heavy-duty vehicles.

28.5. Clinical Assessment

Clinical assessment should focus on identifying potentially at-risk drivers, with history focused on whether the driver has, within the past 12 months, experienced a severe hypoglycaemic event, has hypoglycaemic unawareness, or has comorbidities and complications of diabetes that may interfere with driving.[8,9]

28.5.1 Hypoglycaemia

Drivers who experience a "severe hypoglycaemic event" (defined as an event requiring external assistance, or resulting in loss of consciousness or seizure) while driving, should ideally not drive until cleared by a medical practitioner.

Assessment should focus on establishing the cause and future risks of hypoglycaemia. Patient education (Figure II) is imperative and medication changes may be required. Factors resulting in hypoglycaemia include amongst others non-adherence or alteration to medication, unexpected exertion, alcohol intake, or irregular meals. Meal regularity and variability in medication administration may be important considerations for long-distance commercial driving or for drivers operating in shifts. Excessively tight control may contribute to hypoglycaemia.

28.5.2 Non-driving period after a 'severe hypoglycaemic event'

If a severe hypoglycaemic event occurs, the person should not drive for a minimum period of six weeks thereafter. It takes many weeks for patterns of glucose control and behaviour to be re-established and for any temporary 'reduced awareness of hypoglycaemia' to resolve. The non-driving period should be individualised and will depend on factors such as identifying the reason for the episode, and the type of driving. Recommendation for return to driving should be based on patient behaviour and objective measures of glycaemic control (documented blood glucose) over a reasonable time interval.

28.5.3 Reduced awareness of hypoglycaemia

Reduced awareness of hypoglycaemia markedly increases the risk of a severe hypoglycaemic event and is therefore a risk for road safety. It may be screened for using the Clarke questionnaire[10] which is particularly useful for people with insulin-treated diabetes of longer duration (more than 10 years), or following a severe hypoglycaemic event or after a crash.

Any driver who has a persistent reduced awareness of hypoglycaemia is not fit to drive unless their ability to experience early warning symptoms returns or they have an effective management strategy for lack of early warning symptoms.

28.5.4 Acute hyperglycaemia

While acute hyperglycaemia may affect some aspects of brain function, there is insufficient evidence to determine regular effects on driving performance and related crash risk. Each person with diabetes should be counselled about management of their diabetes during days when they are unwell and should be advised not to drive if they are acutely unwell with metabolically unstable diabetes.

28.5.5 Comorbidities and end-organ complications

Assessment and management of comorbidities is an important aspect of managing people with diabetes with respect to their fitness to drive. This should be part of routine review as per recommended practice and may include but is not limited to vision, neuropathy and foot care, neurological conditions, musculoskeletal conditions, sleep apnoea and cardiovascular conditions.

Author: Peter J Raubenheimer

Editors: Nazeer A Mohamed and Aslam Amod

References

1. ADA Position Statement. Diabetes and Driving. Diabetes Care 2014; 37(S1):97-S103.
2. Diabetes and Driving: 2015 Canadian Diabetes Association Updated Recommendations for Private and Commercial Drivers. Houlden RJ, Berard L, Cheng A et al. Canadian J of Diabetes 2015;39:347-353
3. Cox DJ, Gonder-Frederick L, Kovatchev B, Jullian D, Clarke W. Driving decrements in type I diabetes during moderate hypoglycemia. Diabetes. 1993;42:239–43
4. CoxD, Gonder-FrederickL, KovatchevB, JulianD, ClarkeW. Progressive hypoglycemia's impact on driving simulation performance. Occurrence, awareness and correction. Diabetes Care 2000; 23: 163-70.
5. ECRI Diabetes and Commercial Motor Vehicle Safety (Federal Motor Carrier Safety Administration). June 2011 Update. Plymouth Meeting, Pennsylvania, ECRI, 2011.
6. Laberge-Nadeau C, Dionne G, Ekoé JM, et al. Impact of diabetes on crash risks of truck-permit holders and commercial drivers. Diabetes Care 2000;23:612–617
7. Tregear SJ, Rizzo M, Tiller M, et al. Diabetes and motor vehicle crashes: a systematic evidence-based review and meta-analysis. In Proceedings of the Fourth International Driving Symposium on Human Factors in Driver Assessment, Training and Vehicle Design. Iowa City, Iowa, The University of Iowa, 2007, p. 343–35
8. National Transport System of Australia. Assessing Fitness to Drive 2016. https://static.diabetesaustralia.com.au/s/fileassets/diabetes-australia/17bc68dd-2414-496c-86fe-dcd5d689882e.pdf accessed 13Feb 2017.
9. Diabetes Mellitus: Assessing Fitness to Drive. DVLA United Kingdom. March 2016. https://www.gov.uk/guidance/diabetes-mellitus-assessing-fitness-to-drive. Accessed 13 Feb 2017.
10. Clarke W, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. Diabetes Care. 1995; 18(4): 517–522.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Chapter 29: Male sexual dysfunction in type 2 diabetes

SEMDSA Type 2 Diabetes Guidelines Expert Committee

SEMDSA 2017 Recommendations	
Screen all adult men with type 2 diabetes regularly for ED with a sexual function history or questionnaire. Erectile dysfunction (ED) is common in adult men with type 2 diabetes, significantly impacts quality of life, and is a risk factor for cardiovascular disease and mortality.	B
All men with type 2 diabetes and ED or other symptoms of hypogonadism should be investigated for hypogonadism. Measure total testosterone (and free testosterone) between 7am and 11am, preferably in the fasting state.	B
Offer hypogonadal men testosterone therapy (TTh). Monitor therapy regularly with symptom assessment, digital rectal examination, prostate specific antigen, haematocrit and testosterone levels.	
A PDE5 inhibitor is the initial treatment of choice for eugonadal men with ED (if not contraindicated).	
Men with ED who fail to respond to PDE5 inhibitor therapy (with or without TTh) should be referred to a specialist in male sexual dysfunction (urologist or specialist in sexual medicine) for alternative treatment.	C
Men with hypogonadism or ejaculatory disorders who desire fertility should be referred to a specialist with experience in this field.	C

Refer to Appendix 29 for an overview of the approach to male sexual dysfunction.

29.1 Erectile Dysfunction

29.1.1 Epidemiology

Erectile dysfunction (ED), defined as the inability to sustain adequate penile erection for satisfactory sexual activity, is common in adult men with T2DM (50 to 75%)[1] and negatively impacts quality of life.[2,3] ED has also been described in up to 1/3 of *newly diagnosed* men with diabetes.[4] Additional risk factors for ED include diabetes duration, increasing age, poor glycaemic control, cigarette smoking, hypertension, dyslipidemia, androgen deficiency states and cardiovascular disease (CVD). ED occurs 10–15 years earlier in men with diabetes, is more severe and less responsive to oral drugs.[3]

29.1.2 Pathophysiology

An erection is a neurovascular event requiring intact neural pathways and normal endothelial function. Diabetes mellitus is frequently associated with micro and macrovascular complications which contribute to ED. Endothelial dysfunction is thought to play a major role and accounts for the consistent association between ED and cardiovascular disease risk and mortality.[5-7] Though there are no randomised clinical trials demonstrating reduced incidence or altered progression of ED with management of the hyperglycaemia, there is data from the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study indicating that better glycaemic control leads to reductions in peripheral neuropathy. Peripheral neuropathy impairs sensory feedback from the penis resulting in erectile dysfunction. Though there is conflicting data regarding diet, glycaemic control and ED, it is advisable to improve glycaemic control as a potential factor for maintaining erectile function in these individuals. In addition, psychological factors, such as depression, performance anxiety and relationship factors may contribute to ED e.g. depression was present in 28% of men with T2DM in a large meta-analysis of 51,331 patients from 10 controlled studies. [8]

The multitude of factors contributing to ED in type 2 diabetes is listed in Table I.

Table I: Mechanisms associated with ED in type 2 diabetes[9]

Autonomic neuropathy
Peripheral neuropathy
Hypertension and therapies
Peripheral vascular disease
Hyperlipidaemia
Drug-related side effects
Cavernosal smooth muscle disorder
Hypogonadism with reduced sexual desire (double risk)
Psychological factors including depression
Ejaculatory disorders
Retrograde ejaculation /anejaculation
Reduced sensation

29.1.3 Screening

Adult males with type 2 diabetes should be screened regularly for ED. A sexual function history may be sufficient, but a number of validated questionnaires exist and have been shown to be sensitive and specific for determining presence of ED and providing a means of assessing response to therapy.[10] The 5-item version of the International Index of Erectile Function (IIEF-5)

Table II: The International Index of Erectile Function (IIEF-5) Questionnaire[11]

Over the past 6 months:					
1. How do you rate your **confidence** that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, **how often** were your erections hard enough for penetration?	Almost never / never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5
3. During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/ never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5
4. During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, **how often** was it satisfactory for you?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5

IIEF-5 scoring:
The IIEF-5 score is the sum of the ordinal responses to the 5 items.
22-25: No erectile dysfunction
17-21: Mild erectile dysfunction
12-16: Mild to moderate erectile dysfunction
8-11: Moderate erectile dysfunction
5-7: Severe erectile dysfunction

is shown in Table II. A detailed history is the cornerstone of the evaluation of sexual dysfunction and ED but must be sensitive to the patient's personal, cultural and ethnic background. Having the partner attend and engage in the clinical interview assists in clarifying symptoms and refining the diagnosis. Identifying potentially reversible causes of ED is important (e.g. drugs, depression).

Recommended blood tests include HbA_{1c}, lipid profile and serum testosterone. An effort ECG is advised if there is a family history of premature cardiovascular disease.

29.1.4 Treatment

Treatment of ED should occur concurrently with lifestyle modification along with treatment of organic (e.g. neuropathy or vasculopathy) and psycho-sexual dysfunctions (e.g. depression and/or anxiety).

PDE 5 inhibitors are the cornerstone of therapy for ED, and if there are no contraindications, should be offered as first-line therapy to men with diabetes in the absence of hypogonadism.[12-14] PDE5 inhibitors are absolutely contraindicated with concurrent nitrate use. They are safe to use in men with stable ischaemic heart disease who are not using nitrates, and may actually be beneficial for ischaemic heart disease, peripheral neuropathy and nephropathy.[9] Men with diabetes generally need the higher dose PDE5 inhibitor, and about 50% will have an adequate response to therapy.

Patients who fail adequate on demand or daily dosing with a PDE 5 inhibitor therapy should be referred to a specialist (sexual medicine or urologist) for second-line therapies such as vacuum constriction devices, intracorporal injection therapy with prostaglandin E1 and/ or papaverine and phentolamine. In some cases a penile prosthesis may be considered. Treatment of hypogonadism prior to initiating therapy with phosphodiesterase type 5 (PDE5) inhibitors decreases the number of non-responders.[15,16]

29.2 Hypogonadism

29.2.1 Risk factors for hypogonadism

T2DM is a risk factor for hypogonadism.[17] While it is advisable to measure testosterone levels in all adult males with T2DM (it is estimated that up to 40% have hypogonadism),[9] it is mandatory to measure total and/or free testosterone levels in all individuals with symptoms of hypogonadism/low libido (decrease in sexual thoughts), poor morning erections as well as erectile dysfunction. The presence of non-sexual symptoms (low mood, fatigue, lack of vitality and cognitive impairment) should also necessitate measurement.[18] Additional considerations for measurement are all patients with obesity and features of the metabolic syndrome, osteopaenia or osteoporosis, vitamin D deficiency, hypertension and the use of glucocorticoids, opioids or antipsychotics.[19,20] The overlapping symptoms of hypogonadism with hypothyroidism necessitate the assessment of TSH.[21,22]A prolactin level is useful to exclude primary pituitary disorders.

Hypogonadism associated with metabolic disorders such as T2DM and obesity usually results from hypogonadotrophic hypogonadism; The LH and FSH levels are usually low or inappropriately normal in this situation and pituitary imaging is usually not necessary in the absence of other features of hypopituitarism. Addressing metabolic parameters and obesity may allow for recovery of the hypogonadism. This is unlike age-related hypogonadism or more permanent conditions, such as pituitary or testicular disease, which will necessitate lifelong testosterone therapy (TTh).

29.2.2 Diagnosis and laboratory testing

The diagnosis of hypogonadism requires the presence of symptoms and signs of androgen deficiency (impaired cognitive and sexual function, often in association with depressive symptoms) together with decreased serum testosterone concentration. The recommended laboratory tests for confirming the diagnosis are serum total testosterone (TT) and free testosterone. Equilibrium dialysis is the gold standard for measurement of free testosterone, but in South Africa a calculated free testosterone is widely used - this requires measurement of serum SHBG and TT and is considered acceptable for determining free testosterone levels.[23] Testosterone secretion shows diurnal variation so the preferred time for sampling for TT measurement is 7h00 -11h00, preferably after an overnight fast. Despite diurnal variation being substantially blunted in older men[24] and possibly in symptomatic hypogonadal men regardless of age, the same sampling time is recommended.[24] A serum prolactin measurement is indicated when TT level <5.2 nmol/L or secondary hypogonadism is suspected. Additional tests include LH, to differentiate between primary and secondary hypogonadism, TSH and vitamin D should also be measured as there is overlap of symptoms of hypothyroidism and hypogonadism, and vitamin D deficiency is a risk factor for hypogonadism.[19,20]

Though measurement of TT is widely accepted as a diagnostic test for hypogonadism, there is no consensus on the definition of testosterone deficiency based on the lower TT threshold. The International Society for the Study of the Ageing Male (ISSAM) Hypogonadism panel recommend a cut off of 12.1 nmol/L,[25] while the European Male Ageing Study (EMAS) recommended a threshold of 11 nmol/L.[26] Hypogonadal symptom prevalence increases with TT levels <12.1 nmol /L.[18] Testosterone receptor sensitivity varies between individuals which may account for differing degrees of hypogonadal symptoms and variable levels of TT.[27] The free testosterone should be evaluated In individuals with hypogonadal symptoms and normal TT and TSH levels. Differing lower thresholds for free testosterone have been recommended with 225 pmol/L being the lowest[28] and 347 pmol /L being suggested by others.[29,30] Regardless of the level used, the diagnosis of hypogonadism is only confirmed if symptoms are present.

29.2.3 Treatment

Testosterone therapy (TTh) is approved for the treatment of hypogonadism. A trial of therapy for 3 to 6 months may be considered in patients with uncertain diagnostic levels of serum testosterone, though 12 months TTh may be required to fully assess response.[1] The patient should be given the opportunity to actively participate in the choice of testosterone formulation. Patients with inadequate therapeutic responses to TTh should be referred for further investigation of other causes for sexual dysfunction. T2DM men with hypogonadism who wish to maintain their fertility, now or in the future, should receive other forms of therapy (not TTh) and be referred to a healthcare professional with expertise in managing these men .

TTh options are oral and intramuscular and include:

Testosterone undecanoate

Oral, 3 to 4 capsules in divided doses daily. Absorption is through the lymphatic system, with consequent reduction of liver involvement.

Intramuscular injection is initiated after measurement of testosterone levels; depending on testosterone levels and severity of hypogonadal symptoms the interval to the 2nd injection may be reduced and given at 6 weeks with subsequent injections every 10-14 weeks. This allows for a more rapid achievement of the steady-state testosterone levels which are achieved with this form of testosterone without fluctuation.[34] Long-acting preparations cannot allow early drug withdrawal in case of side effects.[33]

Testosterone cypionate

One injection every 2-3 weeks. Short-acting preparation that allows drug withdrawal in case of onset of side-effects. Possible fluctuation of testosterone levels.[31,32]

Testosterone enanthate

One injection every 2-3 weeks. Short-acting preparation that allows drug withdrawal in case of onset of side-effects. Fluctuation of testosterone levels.[31,32]

29.2.4 Monitoring

Monitoring after initiation of TTh includes the assessment of symptom resolution, side-effects, serum testosterone levels, prostate specific antigen (PSA), haematocrit and regular digital rectal examination(DRE); the suggested monitoring interval is 3, 6 and then 12 months post-initiation and annually thereafter, and is also dependent on the formulation of TTh used.

Insufficient data exists for determination of the optimal target serum testosterone; hence the recommendation is for maintenance of levels within the normal range. Due to variability in laboratory values the same laboratory should be used for measurement.[25] Testosterone levels should be measured towards the end of the injection interval (trough level) regardless of the preparation and levels below the normal range should receive dosing at shorter injection intervals; for testosterone levels above the normal range extension of the injection interval or dose reduction must be considered.[34]

Concerns exist about a link between prostate cancer and testosterone therapy: recent evidence fails to support this concern or that TTh is associated with growth of subclinical prostatic lesions.[35,36] It is still recommended that patients undergo prostate assessment prior to commencement of therapy, including a PSA and digital rectal examination (DRE). The presence of abnormalities on DRE or elevated PSA may warrant ultrasound guided prostatic biopsy, and these patients should be referred to a urologist for further assessment.

Polycythaemia and haematocrit

Follow up should include haematological assessment with maintenance haematocrit levels below 54%. There does not appear to be an increase in cardiovascular events with the elevated haematocrit possibly on the basis of vasodilator and

anti-atherosclerotic effects, but levels repeatedly in excess of 54% require therapeutic phlebotomy with or without discontinuation of TTh. [37]

29.2.5 Hypogonadism and cardiovascular disease

Numerous studies have shown an association between low testosterone levels and increased cardiovascular risk and mortality. An observational study from Italy which included 1687 patients managed for erectile dysfunction showed that the risk for major adverse cardiovascular events after adjustment for age and chronic diseases was 20% higher when testosterone levels were < 8 nmol/L.[38] The Copenhagen Heart Study showed that reductions of total testosterone below the 10th percentile increased risk of ischaemic stroke by 34% when compared to normal testosterone individuals.[39] There does appear to be an association between testosterone levels and glycaemic control in type 2 diabetes, suggesting that better glycaemic control is beneficial for maintaining testosterone levels.[40] TTh improves surrogates markers of cardio metabolic risk, including fasting plasma glucose, triglycerides and waist circumference.[41]

29.2.5 Therapy outcomes

Resolution of hypogonadal signs and symptoms occur at variable times for different organ systems.[42] Libido, vigor and depression as well as quality-of-life measures can expect to improve from 3 to 4 weeks following commencement of therapy, although erectile and ejaculatory function may require up to 12 months of TTh to improve.[1] Decreased fat mass and increased lean body mass and muscle strength and improvement in insulin sensitivity may be apparent about 3 to 4 months after initiation of TTh. Improvements in bone are detectable from 6 months, but the full beneficial effect may take between 2 and 6 years.[43]

29.3 Ejaculatory disorders

These are common as part of the spectrum of sexual dysfunction in men with diabetes occurring in 32 to 67% of the male diabetic cohort and require enquiry as recognition of these is an important component in sexual quality of life. Disorders include retrograde ejaculation with incomplete closure of the bladder neck during ejaculation usually secondary to autonomic neuropathy, premature ejaculation and retarded ejaculation.[44]

29.4 Peyronies Disease

Peyronies disease presents with a fibrotic plaque within the tunica albuginea of the penis leading to penile shortening, curvature and sexual dysfunction in approximately 20% of diabetic males with ED. 15% of men with Peyronies disease have concomitant Duputyrens contracture. Surgery remains the gold standard for correcting erect penile deformity in men with stable disease.

Authors: Padaruth Ramlachan and Tanya E Kinvig
Editor: Aslam Amod

References

1. Hackett G, Cole N, Bhartia M, et al. Blast Study Group. The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study). Int J Clin Pract 2014; 68:203–15.
2. Eardley I, Fisher W, Rosen RC, et al. The multinational Men's Attitudes to Life Events and Sexuality study: the influence of diabetes on self-reported erectile function, attitudes and treatment seeking patterns in men with erectile dysfunction. Int J Clin Pract 2007; 61:1446-53
3. Esposito K, Maiorino MI, Bellastella G. Diabetes and sexual dysfunction: current perspectives. Diabetes, Metab Syndr Obes Targets Ther. 2014;7:95. doi:10.2147/DMSO.S36455.
4. Al-Hunayan A, Al-Mutar M, Kehinde EO, et al. The prevalence and predictors of erectile dysfunction in men with newly diagnosed type 2 diabetes mellitus. BJU Int 2007; 99:130-4
5. Dong J.Y., Zhang Y.H., Qin L.Q. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol. 2011;58:1378–1385.
6. Vlachopoulos C.V., Terentes-Printzios D.G., Ioakeimidis N.K., Aznaouridis K.A., Stefanadis C.I. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. Circ Cardiovasc Qual Outcomes. 2013;6:1–11
7. Gazzaruso C. Erectile dysfunction and coronary atherothrombosis in diabetic patients: pathophysiology, clinical features and treatment. Expert Rev Cardiovasc Ther 2006;4:173–80. doi:10.1586/14779072.4.2.173
8. Ali S, Stone, MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabet Med 2006; 23 (11): 1165-73
9. Hackett G. Should PDE5Is be prescribed routinely for all men with newly diagnosed type 2 diabetes? Br J Diabetes Vasc Dis. 2015;15(4):184-186. doi:10.15277/bjdvd.2015.054.
10. Ramanathan R, Mulhall J, Rao S, et al positive correlation between the International Index of Erectile Function (IIEF) and Sexual Health Inventory for Men (SHIM): implications for calculating a derived SHIM for clinical use. J Sex Med 2007; 4:1334-44
11. Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res. 1999 Dec;11(6):319-26
12. Fonseca V, Seftal A, Denne J, et al. Impact of diabetes mellitus and the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials. Diabetalogia 2004; 47:1914-23
13. Rendell MS, Rajfer J, Wicker PA, et al. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomised controlled trial. JAMA 1999; 281:421-6.
14. Goldstein I, Young JM, Fischer J, et al. Vardenafil a new phosphodiesterase type V inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicentre double-blind, placebo-controlled fixed dose study. Diabetes Care 2003; 26:777-83
15. Shabsigh R, Kaufman JM, Steidle C, et al. Randomised study of testosterone gel as adjunctive therapy to sildenafil and hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol 2004; 172:658-63
16. Kalinchenko SY, Kozlov GI, Gontcharov NP , et al. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. Ageing Male 2003; 6:94-9
17. Mulligan T, Frick MF, Zuraw QC, et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract 2006;60:762–9.
18. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab 2006;91:4335–43
19. Lee DM, Tajar A, Pye SR, et al. The EMAS Study Group. Association of Hypogonadism with vitamin D status: the European Male Ageing Study. Eur J Endocrinol 2012; 166:77–85.
20. Wehr E, Pilz S, Boehm BO, et al. Association of vitamin D status with serum androgen levels in men. Clin Endocrinol 2010; 73:243–8.
21. Bremner AP, Feddema P, Leedman PJ, et al. Age-related changes in thyroid function: a longitudinal study of a community-based cohort. J Clin Endocrinol Metab 2012;97:1554–62
22. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to1994): National Health and Nutrition Examination Survey(NHANES III). J Clin Endocrinol Metab 2002; 87:489–99.
23. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999; 84:3666–72.

24. Crawford ED, Barqawi AB, O'Donnell C, Morgentaler A. The association of time of day and serum testosterone concentration in a large screening population. BJU Int 2007;100:509–13
25. Lunenfeld B, Mskhalaya G, Zitzmann M, et al. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. The Ageing Male 2015; 18 (1): 5-15
26. Wu FC, Tajar A, Beynon JM, et al. EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010; 363:123–35.
27. Zitzmann M. The role of the CAG repeat androgen receptor polymorphism in andrology. Front Horm Res 2009; 37:52–61.
28. (j) Rosner W, Auchus RJ, Azziz R, et al. Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society Position Statement. J Clin Endocrinol Metab 2007;92:405–13.
29. Morgentaler A, Khera M, Maggi M, Zitzmann M. Commentary: who is a candidate for testosterone therapy? A synthesis of international expert opinions. J Sex Med 2014;11:1636–45
30. Kacker R, Hornstein A, Morgentaler A. Free testosterone by direct and calculated measurement versus equilibrium dialysis in a clinical population. Aging Male 2013;16:164–8.
31. Wang C, et al. Pharmacokinetics and safety of long-acting testosterone undecanoate injections in hypogonadal men: an 84-week phase III clinical trial. J Androl 2010; 31(5):457-65.
32. Bhasin S, et al. Clinical review 85: Emerging issues in androgen replacement therapy. J Clin Endocrinol Metab 1997; 82(1):3-8.
33. Andropause: hormone replacement therapy in the ageing male. Eur Urol 2000; 38(6):655-62.
34. https://www.medicines.org.uk/emc/medicine/15661
35. Pastuszak AW, Pearlman AM, Lai WS, et al. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. J Urol 2013; 190:639–44.
36. Morgentaler A, Lipshultz LI, Bennett R, et al. Testosterone therapy in men with untreated prostate cancer. J Urol 2011; 185:1256–60.
37. Jones TH, Saad F. The effects of testosterone on risk factors for, and the mediators of, the atherosclerotic process. Atherosclerosis 2009; 207:318–27.
38. Corona G, Monami M, Boddi V et al. Low testosterone is associated with an increased risk of MACE lethality in subjects with erectile dysfunction. J Sex Med 2010; 7:1557-64.
39. Holmboe SA, Jensen TK, Linneberg A et al. Low testosterone: a risk marker rather than a risk factor Type 2 diabetes JCEM 2016; 101:69-78
40. El-Sakka AI, Sayed HM, Tayeb KA. Androgen pattern in patients with type 2 diabetes-associated erectile dysfunction: impact of metabolic control. Urology 2009; 74:552-9
41. Aversa A, Bruzziches R, Francomano D, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late onset hypogonadism and metabolic syndrome: results from a 24-months, randomized double blind placebo-controlled study. J Sex Med 2010; 7:3495–503.
42. Saad F, Aversa A, Isidori AM, et al. Onset of effects of testosterone treatment and time span until maximum effects are achieved. Eur J Endocrinol 2011;165:675–85.
43. Aversa A, Bruzziches R, Francomano D, et al. Effects of longacting testosterone undecanoate on bone mineral density in middle aged men with late-onset hypogonadism and metabolic syndrome: results from a 36 months controlled study. Aging Male 2012;15: 96–102.
44. Isidro ML. Sexual dysfunction in men with type 2 diabetes. Postgrad Med 2012; 88:152-9

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 1: Epidemiology diabetes surveys in South Africa (glucose-based)

SEMDSA Type 2 Diabetes Guideline Expert Committee

Table 2. Prevalence of diabetes mellitus (D), impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) in cross-sectional community surveys in South Africa, based on World Health Organisation (WHO) and American Diabetes Association (ADA) criteria

Ethnic Group / Province	Author Year	Urban (U) / Rural (R) / Peri-urban (P-U)	n	Age (yr)	Method**	Prevalence (%)†		
						D	IFG	IGT
1985 WHO criteria								
Africans (Black)								
KwaZulu Natal	Omar 1993	U	479	>15	OGTT	5.3	-	7.7
Western Cape	Levitt 1993	U	729	>30	OGTT	8.0	-	7.0
Free State	Mollentze 1995	U	758	≥25	OGTT	6.0	-	12.2
		P-U	853	≥25	OGTT	4.8	-	10.7
Mixed ancestory‡								
Western Cape	Levitt 1999	P-U	974	≥15	OGTT	10.8	-	10.2
Asian Indian								
KwaZulu-Natal	Omar 1994	U	2479	>15	OGTT	13.0	-	6.9
1998 WHO and 1997 / 2003 ADA criteria								
African (Black)								
KwaZulu Natal	Motala 2008	R	1021	>15	OGTT	3.9	1.5	4.8
Western Cape	Peer 2012	U	1099	25-74	OGTT	13.1	1.2	11.2
KwaZulu-Natal	Hird T 2016	U	1190	≥ 18	OGTT	12.9	0.8	3.5
Mixed ancestory‡								
Western Cape	Erasmus 2012	U	642	≥31	OGTT	26.3	3.2	15.0

**OGTT: 75g oral glucose tolerance test;
†Age-adjusted prevalence
‡Khoi - East Indian - Europid.

Reference

Mbanya JCN, Motala AA, Sobngwi E, Assah FK, Enoru ST. Diabetes in sub-Saharan Africa. Lancet. 2010;375(9733):2254-2266. doi:10.1016/S0140-6736(10)60550-8.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Appendix 2: The South African National Health and Nutrition Examination Survey-1 (SANHANES-1)

Prevalence (mean %) of metabolic syndrome features in persons >15 years

	Male	Female	45-54 yrs	55-64 yrs	65+ yrs	African	White	Coloured	Asian	Total
LIPID PROFILE										
TC > 5.0 mmol/l	18.9	28.1	37.6	41.3	43.2	20.6	55.5	34.2	43.4	**23.9**
HDL > 1.2 mmol/l	52.5	44.1	49.3	42.5	45.9	49.0	32.1	44.7	52.9	**47.9**
LDL > 3.0 mmol/l	18.6	29.6	36.4	41.4	40.7	21.5	50.3	34.3	48.6	**24.6**
Trig > 1.7 mmol/l	28.3	21.3	41.2	36.7	37.4	22.0	56.2	29.7	45.7	**24.5**
BLOOD PRESSURE										
BP >140/90 mmHg	10.2	10.2	19.5	21.5	18.9	9.9	12.2	11.8	7.3	**10.2***
GLYCAEMIA										
HbA_{1c} > 6.5%	7.9	11.0	16.7	24.4	19.0	8.2	8.1	13.4	30.7	**9.5**
HbA_{1c} 6.1 - 6.5%	7.7	10.0	11.2	13.9	19.9	8.7	4.0	11.2	11.1	**8.9**
BMI MALES										
BMI 25 - 29.9 kg/m2			31.2	25.9	40.4	19.1	§	22.1	32.2	**20.1**
BMI > 29.9 kg/m2			18.7	19.3	13.1	9.4	§	15.1	7.6	**10.6**
WAIST CIRCUMFERENCE MALES										
Waist > 94 cm			39.9	34.1	39.7	17.4	§	25.7	36.9	**20.2**
Waist > 102 cm			22.1	16.3	16.1	8.0	§	12.0	24.3	**9.8**
BMI FEMALES										
BMI 25 - 29.9 kg/m^2			21.2	27.6	23.1	24.9	§	24.4	22.8	**24.8**
BMI > 29.9 kg/m^2			56.3	52.2	46.9	39.9	§	34.9	32.4	**39.2**
WAIST CIRCUMFERENCE FEMALES										
Waist > 80 cm			81.7	85.5	79.8	67.6	§	67.2	79.5	**68.2**
Waist > 88 cm			69.9	70.0	60.3	51.1	§	49.9	54.1	**50.8**

TC=total cholesterol; HDL=High density lipoprotein; LDL=low density lipoprotein; Trig=triglycerides; BP= blood pressure; BMI=body mass index;
*The prevalence of hypertension including those on treatment was 31%.
§=insufficient data for analysis

With South Africa's epidemiological transition from infectious diseases to non-communicable diseases (NCDs) there is a great need for a better understanding of both the prevalence of NCDs and the associated risk factors among South Africans, and a need to translate such information into effective health policies, health programmes and services. It is with this backdrop that the Human Science Research Council, in partnership with the Medical Research Council and several major universities embarked on the SANHANES in 2012. The plan was to recruit and establish a nationally representative cohort of 5000 South African households to be followed up over the coming years. The first cross-sectional examination (SANHANES-1) using a multi-stage disproportionate, stratified cluster sampling approach was completed in 2012 and reported in 2014.

The final population sample included 25 532 people from 6305 households who were interviewed, and then subsequently invited to a clinic examination and blood biomarker analyses for lipid profiling and HbA_{1c}. The results for the prevalence of anthropometric, blood pressure, lipid and HbA1c abnormalities are summarised here.

Reference

1. Shisana O, Labadarios D, Rehle T, et al. South African National Health and Nutrition Examination Survey, 2012 (SANHANES-1). In: 2014th ed. Cape Town: HSRC Press; 2014:1-397.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 3: The use of HbA_{1c} for the diagnosis of type 2 diabetes

SEMDSA Type 2 Diabetes Guideline Expert Committee

Use of HbA_{1c} in the diagnosis of diabetes mellitus

For the diagnosis of diabetes	• $HbA_{1c} \geq 6.5\%$ (48 mmol/mol) • $HbA_{1c} < 6.5\%$ does not exclude diagnosis by blood glucose • Glucose–based tests (FPG, OGTT) are still valid
Interpretation of $HbA_{1c} < 6.5\%$	• No recommendation because of insufficient evidence
Requirements to fulfill (provisos) for use of HbA_{1c} for diagnosis	• Stringent quality assurance tests in place[a] • Assays standardised to criteria aligned with international reference values[b] • Low cost and wide availability • No conditions present which preclude accurate measurement (Table III)
Choice between HbA_{1c} and plasma glucose should be based on local considerations	• Cost • Availability of equipment • National quality-assurance system • Population characteristics (e.g. prevalence of malaria or haemoglobinopathies) • Crucial to ensure that accurate blood glucose measurement be generally available at primary healthcare level before introducing HbA_{1c} measurement as a diagnostic tool

[a] Appropriate conditions for assay method: Standardised assay; Low coefficient of variability; Calibrated against International Federation of Clinical Chemists (IFCC) standards
[b] DCCT aligned and NGSP certified

Factors which influence HbA_{1c} measurement

Erythropoiesis	Increased HbA_{1c}	Iron deficiency, vitamin B_{12} deficiency, decreased erythropoiesis
	Decreased HbA_{1c}	Administration of erythropoietin, iron or vitamin B_{12}, reticulocytosis, chronic liver disease
Altered haemoglobin	Variable HbA_{1c}	Genetic or chemical alterations in haemoglobin may increase or decrease HbA_{1c}: Haemoglobinopathies, HbF, methaemoglobin
Glycation	Increased HbA_{1c}	Alcoholism, chronic renal failure, decreased intra-erythrocyte pH
	Decreased HbA_{1c}	Aspirin, vitamins C and E, certain haemoglobinopathies, increased intra-erythrocyte pH
	Variable HbA_{1c}	Genetic determinants
Erythrocyte destruction	Increased HbA_{1c}	With increased erythrocyte life span: Splenectomy
	Decreased HbA_{1c}	With decreased erythrocyte life span: Haemoglobinopathies, splenomegaly, rheumatoid arthritis, drugs (e.g. antiretrovirals, ribavirin, dapsone)
Assays	Increased HbA_{1c}	Hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use
	Decreased HbA_{1c}	Hypertriglyceridaemia
	Variable HbA_{1c}	Haemoglobinopathies

Note: Some of these factors cannot be detected by certain assays

Reference

1. World Health Organization. Use of glycated haemoglobin (HbA_{1c}) in the diagnosis of diabetes mellitus: http://www.who.int/diabetes/publications/reporhba1c_2011.pdf. (accessed 25 January 2016).

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 9.1: Drug review: Metformin

SEMDSA Type 2 Diabetes Guideline Expert Committee

Metformin, a biguanide, was isolated from Galega officinalis (goats rue), which was used to treat symptoms characteristic of diabetes mellitus in medieval times. French diabetologist Jean Sterne was the first to publish studies about its glucose lowering effect in humans in 1957, when he dubbed the drug "gluco-phage" (glucose-eater).[1] The common occurrence of lactic acidosis with other biguanides has led to their withdrawal, and metformin is currently the only commercially available biguanide. It has been registered in the United Kingdom since 1958, in the United States since 1994 and in South Africa since August 1974. Metformin is the most commonly used oral therapy for the treatment of type 2 diabetes worldwide and forms the backbone of treatment in most published guidelines.

9.1.1 Mechanism of action

(Optional reading)

The exact mechanisms of action of metformin have been debated. The predominant anti-hyperglycaemic effect was thought to be through the reduction in hepatic glucose production and increased insulin-mediated glucose uptake by skeletal muscle. However, the importance of its gut based mechanism of action is gaining significance.[2,3]

Reduced hepatic glucose output is thought to be mediated through inhibition of liver mitochondrial electron transport, leading to activation of the enzyme AMP-activated protein kinase. Increased cellular AMP leads to blockade of glucagon-dependent hepatic glucose production as well as direct inhibition of gluconeogenesis through inhibition of a key enzyme, fructose-1,6-bisphosphatase.

At the level of skeletal muscle, increase in glucagon receptor–stimulated adenylate cyclase has been shown to increase glucose transporter activity (GLUT-4) and glucose uptake.

Gut effects include the stimulation of jejunal enteroendocrine L-cells to produce glucagon-like peptide-1 (GLP-1) and peptide YY, alteration of bile acid metabolism and the gut microbiome, as well as delayed and reduced glucose absorption.[2–4] The increase in GLP-1 levels with metformin are similar to those seen with DPP-4 inhibitors.[5] Recent observations that smaller doses of delayed-release metformin (Met-DR), which increases drug delivery to the ileum, is as effective as higher doses of immediate release metformin (Met-I) and extended-release metformin (Met-XR), suggests that gut may be the major target for metformin action. Suppression of hepatic glucose output may in fact be neuro-humorally mediated via the gut.[3,6]

Peripheral effects include the stimulation of fatty acid oxidation and an increase in systemic measures of insulin sensitivity (as is common with many glucose lowering therapies). However, the role of metformin in insulin-mediated glucose uptake is not proven, and therefore, contrary to popular belief, cannot be classified as an insulin sensitiser.[7,8]

9.1.2 Glycaemic efficacy[9,10,11]

Systematic reviews and meta-analyses of randomised controlled trials show that:

- Metformin monotherapy lowers HbA_{1c} by a mean of -1.1% to -1.3% compared to placebo or diet alone (range from -0.5% to -1.8% for daily metformin doses ranging from 500 mg to 3000 mg).
- Metformin added to other oral therapies lowers HbA_{1c} by a mean of 0.9% compared to placebo.
- Metformin added to insulin therapy lowers HbA_{1c} by a mean of 0.8% compared to insulin alone.

9.1.3 Hypoglycaemia

Hypoglycaemia does not occur in patients (with or without diabetes) receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulphonylureas and insulin) or ethanol.[4] UKPDS 34 reported no cases of severe hypoglycaemia in patients taking metformin alone.[12]

9.1.4 Weight

In the UKPDS metformin monotherapy was not associated with weight gain compared to diet alone group over 10.7 years of follow-up.[12] Meta-analyses confirm that metformin is weight neutral and may result in modest weight loss (mean -1.2 kg) in some patients.

Although uncommon, metformin can occasionally result in anorexia and marked weight loss (cachexia), particularly in older non-obese patients. Unexplained severe weight loss warrants further investigation to exclude other causes.[13] Cessation of metformin therapy leads to weight regain in the absence of other causes.

9.1.5 Microvascular and macrovascular outcome studies

The UKPDS demonstrated significant reductions in diabetes-related deaths, all cause mortality and myocardial infarction in the 342 newly diagnosed obese type 2 diabetes patients randomized to metformin compared to the 411 obese patients

randomised to conventional therapy. Despite a trend, there was no significant reduction in microvascular endpoints.[12]

In a secondary analysis comparing metformin treatment with sulphonylureas (chlorpropamide and glibenclamide) and insulin treated obese patients, metformin significantly reduced all cause mortality and strokes, but *not* myocardial infarction or diabetes-related deaths.[12]

In a supplementary UKPDS trial, 537 obese and non-obese patients inadequately controlled with maximal doses of sulphonylureas were randomly assigned to continue sulphonylureas alone or to add metformin therapy.[12] The addition of metformin resulted in an unexpected 96% increase in diabetes related deaths. The investigators suggested that this was due to an unexpectedly low mortality in the sulphonylurea-only cohort, and added that an epidemiological assessment in 4416 patients did not show an increased risk in diabetes-related death in patients treated with a combination of sulphonylurea and metformin.[12] Nevertheless, these results have raised concerns about the sulphonylurea-metformin combination. Subsequent studies addressing this issue have yielded conflicting results, with some confirming the higher cardiovascular risk with the sulphonylurea-metformin combination

Subsequent systematic reviews, observational, population and prospective studies to clarify the monotherapy benefit of metformin, or its potential cardiovascular risk with sulphonylurea therapy have unfortunately yielded conflicting results, with some reporting lower and others reporting higher risks.[11,14–21] The balance of evidence from these, and prospective randomized trials favours cardiovascular safety and probable benefit with metformin monotherapy compared to placebo. The controversy over metformin-sulphonylurea combinations is addressed in the section on sulphonylureas.

9.1.6 Non-glycaemic benefits

Lipids: Metformin has a favourable effect on lipid profile when compared to placebo, sulphonylureas and insulin. It significantly reduces total cholesterol, LDL-cholesterol and triglycerides and increases HDL-cholesterol.[11,22–24]

Cancer: Population studies have shown that metformin is associated with a significant reduction of cancers (breast and prostate, in particular).[23,25] The exact mechanism of tumour suppression is not known.

Heart Failure: Despite the package insert listing heart failure (HF) as a contraindication, metformin several retrospective studies have reported a lower risk of all-cause death and hospitalisations in diabetes patients with HF.[26–28]

Other: Laboratory studies have shown that metformin may have beneficial anti-inflammatory, anti-coagulant and anti-oxidative effects, and may improve endothelial dysfunction and tumour suppression.[23,24]

9.1.7 Adverse Effects and Special Precautions

Gastrointestinal (GI) side effects: GI disturbances are the commonest side effects of metformin, occurring in 20-30% of users, and is not dose dependent.[24,29] These include abdominal pain, nausea, vomiting, diarrhoea, bloating, taste disturbances and appetite loss. GI tolerability is improved when the metformin dose is up-titrated gradually but about 7% of patients using metformin will discontinue therapy due to GI disturbances.[29] The extended-release formulation, apart from offering improved compliance with once daily dosing, may also improve GI tolerability in some patients.[30] We can find no evidence that film-coated (FC) tablets have any advantage for GI disturbances.

Vitamin B12 (cobalamin or B12) deficiency: The prevalence of low serum B_{12} levels among metformin treated patients (10-30%) is higher compared to non-diabetic individuals and those not taking metformin, especially in those receiving higher doses for more than four years.[31–36] Several researchers have recommended routine screening for B_{12} deficiency in metformin treated patients, but there are no formal guidelines on the subject.[36] The mechanism of B_{12} deficiency with metformin is unknown. Postulated mechanisms have included bacterial overgrowth, changes in small bowel motility, changes in bacterial flora, competitive inhibition or inactivation of B_{12} absorption, or an effect of calcium on cell membranes.[37,38] Recent advances in assessing true B_{12} deficiency (measuring methylmalonic acid (MMA) and homocysteine) has called into question our assessment of B_{12} insufficiency and deficiency with metformin. True B_{12} deficiency should be associated elevated levels of plasma MMA and homocysteine.[39] However, in some studies where these were measured, this has not been the case, implying that the potential mechanism for low serum levels of B_{12} might be an increased uptake and intracellular accumulation of B_{12}.[40] This may well explain why previous reports of low levels of serum B_{12} have usually not been associated with the typical haematological or clinical features of B_{12} deficiency.[23,31,41,42] In controlled clinical trials, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease is very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation.[4]

The clinical relevance of low serum B_{12} levels in metformin treated patients warrants further research. Until there is further clarity, routine screening or prophylaxis for B_{12} deficiency is not recommended; however it should be measured in patients with other risk factors for B12 deficiency, and in those with anaemia or neuropathy. Patients suspected of having clinical B_{12} deficiency should be evaluated with measurement of serum B_{12} and at least one marker of intracellular B_{12} status. If the latter measurement is not available, one should correct the serum deficiency of this inexpensive vitamin using high dose intramuscular injections, as the amount available in general multivitamins (6 µg) may not be enough to correct the biochemical deficiency.[43]

Lactic acidosis: Biguanides have gained notoriety for lactic acidosis but this appears to have little justification for metformin. Large database analyses have shown that the incidence of lactic acidosis is about 4 cases per 100000 person years for metformin users versus 5 cases per 100000 person years for non-metformin users.[44–46] Metformin therapy has not been associated with higher rates of lactic acidosis, and may actually improve outcomes, in

patients with acute myocardial infarction, heart failure, mild-moderate renal failure and liver disease.[28,45,47,48] However, the drug should not be prescribed in patients with the most severe forms of these diseases.

The suggested blanket precaution of withholding metformin therapy prior to and after the administration of iodinated contrast media or general anaesthesia is historical. The reassessment of the risks of lactic acidosis has led the U.S Food and Drug Administration (FDA) to revise these recommendation for iodinated contrast media.[49] SEMDSA makes similar recommendations for patients undergoing general anaesthesia as well (Table I).

Table I: Recommendations for metformin with iodinated contrast media or general anaesthesia

Metformin should be discontinued at the time of or before an iodinated contrast imaging procedure or general anaesthesia in: • Patients with an eGFR between < 60 mL/minute/1.73 m^2 • Patients with a history of liver disease, alcoholism, or heart failure • Patients who will receive intra-arterial iodinated contrast
Re-evaluate eGFR 48 hours after the procedure; restart metformin if renal function is stable and the patient is eating normally.

9.1.8 Dosing and Prescribing

Head to head comparisons of lower metformin doses (1000 mg per day) versus higher doses (2000 mg per day) demonstrate an additional significant reduction of HbA_{1c} by 0.25%.[9] There is debate whether doses higher than 2000 mg per day provide additional glucose lowering. However, the cardiovascular disease benefit observed with metformin therapy in the UKPDS study occurred with a mean daily dose of 2550 mg per day, which justifies this as the reasonable maximal therapeutic dose.[12] The registered maximum total dose for metformin is 3000 mg/day.

Prescribing in chronic kidney disease

The 2012 SEMDSA Guideline[50] recommended a relaxation of the renal contraindications to metformin therapy based on the evidence available at that time[48] (Table II). The FDA has also relaxed its renal recommendations since 2016.[49] Renal function must be monitored at least annually (or more frequently when abnormal) in all patients.

Table II: Metformin recommendations in renal disease

Estimated glomerular filtration rate (eGFR)	Action
≥ 60 ml/minute/1.73 m^2	No renal contraindication to metformin. Monitor renal function annually.
45-59 ml/minute/1.73 m^2	Continue use but increase monitoring of renal function (every six months).
30-44 ml/minute/1.73 m^2	Prescribe metformin with caution. Do not exceed 1 000 mg total daily dose. Closely monitor renal function (every three months).
< 30 ml/minute/1.73 m^2	Stop metformin

9.1.9 Metformin extended-release

The extended-release (XR) formulation of metformin uses a GelShield Diffusion System that allows once daily for doses up to 2000 mg. This reduces the tablet burden and potentially improves adherence and compliance.[51] The outer gel layer of the tablet may be excreted intact resulting in patients noticing ghost tablets in the stool. This, by design, is normal.[52]

When administered once daily is essential that metformin XR be given with the evening meal as the system relies partly on delayed gastric emptying at night.[4,53] Metformin XR offers once daily equivalence for doses ranging from 500 mg to 2000 mg when compared to same daily dose of standard metformin administered two or three times a day.[4,54,55] Administering the 2000 mg dose of metformin XR twice a day showed marginally better placebo-corrected HbA_{1c} reductions (-1.2% vs. -0.9%) but this was not statistically significant.[55]

Although a composite analysis of metformin XR placebo controlled studies show lower rates of diarrhoea, nausea and discontinuations when compared to the composite of standard metformin placebo controlled studies, one cannot draw firm conclusions because they compare different studies.[4,56] In two head-to-head studies adverse events including GI disturbances were similar in patients *initiated* on standard metformin versus the XR.[53,54] However, a number of small studies have shown that when patients with pre-existing GI disturbances with standard metformin are switched to metformin XR, the GI tolerability improves and fewer patients need to discontinue therapy.[30,52,57] GI tolerability of metformin XR also appears to be better in Asian patients with low discontinuation rates (2-4%).[55,58]

Authors: Aslam Amod and Fraser J. Pirie
Editors: Zaheer Bayat, Ankia Coetzee, Nazeer A Mohamed, Joel A Dave, Tanya E Kinvig

References

1. Campbell IW. Metformin -- life begins at 50: A symposium held on the occasion of the 43rd Annual Meeting of the European Association for the Study of Diabetes, Amsterdam, The Netherlands, September 2007. Br J Diabetes Vasc Dis. 2007;7(5):247-252. doi:10.1177/14746514070070051001.
2. Rena G, Pearson ER, Sakamoto K. Molecular mechanism of action of metformin: old or new insights? Diabetologia. 2013;56(9):1898-1906. doi:10.1007/s00125-013-2991-0.
3. Buse JB, DeFronzo RA, Rosenstock J, et al. The Primary Glucose-Lowering Effect of Metformin Resides in the Gut, Not the Circulation. Results From Short-term Pharmacokinetic and 12-Week Dose-Ranging Studies. Diabetes Care. 2015;39(2):dc150488. doi:10.2337/dc15-0488.
4. Glucophage and Glucophage XR [package insert]: Princeton, NJ, USA Bristol Myers Squibb; 2008.
5. Migoya EM, Bergeron R, Miller JL, et al. Dipeptidyl Peptidase-4 Inhibitors Administered in Combination With Metformin Result in an Additive Increase in the Plasma Concentration of Active GLP-1. Clin Pharmacol Ther. 2010;88(6):801-808. doi:10.1038/clpt.2010.184.
6. Scheen AJ. Will delayed release metformin provide better management of diabetes type 2? Expert Opin Pharmacother. 2016;17(5):627-630. doi:10.1517/14656566.2016.1149166.
7. Natali A, Ferrannini E. Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review. Diabetologia. 2006;49(3):434-441. doi:10.1007/s00125-006-0141-7.

8. Soccio RE, Chen ER, Lazar MA. Thiazolidinediones and the Promise of Insulin Sensitization in Type 2 Diabetes. Cell Metab. 2014;20(4):573-591. doi:10.1016/j.cmet.2014.08.005.
9. Hirst JA, Farmer AJ, Ali R, Roberts NW, Stevens RJ. Quantifying the Effect of Metformin Treatment and Dose on Glycemic Control. Diabetes Care. 2012;35(2):446-454. doi:10.2337/dc11-1465.
10. Johansen K. Efficacy of metformin in the treatment of NIDDM. Meta-analysis. Diabetes Care. 1999;22(1):33-37. doi:10.2337/diacare.22.1.33.
11. Sáenz Calvo A, Fernández Esteban I, Mataix Sanjuán A, Ausejo Segura M, Roqué M, Moher D. Metformin for type-2 diabetes mellitus. Systematic review and meta-analysis. Aten primaria. 2005;36(4):183-191.
12. Turner R. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352(9131):854-865. doi:10.1016/S0140-6736(98)07037-8.
13. Metformin and Cachexia - from FDA reports. http://www.ehealthme.com/ds/metformin/cachexia/. Accessed December 27, 2016.
14. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes. JAMA. 2016;316(3):313. doi:10.1001/jama.2016.9400.
15. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Rydén L. Prognostic implications of glucose-lowering treatment in patients with acute myocardial infarction and diabetes: experiences from an extended follow-up of the Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study. Diabetologia. 2011;54(6):1308-1317. doi:10.1007/s00125-011-2084-x.
16. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes, Obes Metab. 2011;13(3):221-228. doi:10.1111/j.1463-1326.2010.01349.x.
17. Fisman EZ, Tenenbaum A, Boyko V, et al. Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. Clin Cardiol. 2001;24(2):151-158.
18. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased Mortality Associated With the Use of Metformin Compared With Sulfonylurea Monotherapy in Type 2 Diabetes. Diabetes Care. 2002;25(12):2244-2248. doi:10.2337/diacare.25.12.2244.
19. Boussageon R, Supper I, Bejan-Angoulvant T, et al. Reappraisal of Metformin Efficacy in the Treatment of Type 2 Diabetes: A Meta-Analysis of Randomised Controlled Trials. Groop L, ed. PLoS Med. 2012;9(4):e1001204. doi:10.1371/journal.pmed.1001204.
20. Sillars B, Davis WA, Hirsch IB, Davis TME. Sulphonylurea-metformin combination therapy, cardiovascular disease and all-cause mortality: the Fremantle Diabetes Study. Diabetes, Obes Metab. 2010;12(9):757-765. doi:10.1111/j.1463-1326.2010.01230.x.
21. Selvin E, Bolen S, Yeh H-C, et al. Cardiovascular Outcomes in Trials of Oral Diabetes Medications. Arch Intern Med. 2008;168(19):2070. doi:10.1001/archinte.168.19.2070.
22. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995;333(9):541-549. doi:10.1056/NEJM199508313330902.
23. Rojas LBA, Gomes MB. Metformin: an old but still the best treatment for type 2 diabetes. Diabetol Metab Syndr. 2013;5(1):6. doi:10.1186/1758-5996-5-6.
24. Ali S, Fonseca V. Overview of metformin: special focus on metformin extended release. Expert Opin Pharmacother. 2012;13(12):1797-1805. doi:10.1517/14656566.2012.705829.
25. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and Cancer: A consensus report. Diabetes Care. 2010;33(7):1674-1685. doi:10.2337/dc10-0666.
26. Papanas N, Maltezos E, Mikhailidis DP. Metformin and heart failure: never say never again. Expert Opin Pharmacother. 2012;13(1):1-8. doi:10.1517/14656566.2012.638283.
27. Rachmani R, Slavachevski I, Levi Z, Zadok B, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. Eur J Intern Med. 2002;13(7):428.
28. Shah DD, Fonarow GC, Horwich TB. Metformin Therapy and Outcomes in Patients With Advanced Systolic Heart Failure and Diabetes. J Card Fail. 2010;16(3):200-206. doi:10.1016/j.cardfail.2009.10.022.
29. McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. Diabetologia. 2016;59(3):426-435. doi:10.1007/s00125-015-3844-9.
30. Blonde L, Dailey GE, Jabbour SA, Reasner CA, Mills DJ. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. Curr Med Res Opin. 2004;20(4):565-572. doi:10.1185/030079904125003278.
31. Ahmed MA, Muntingh G, Rheeder P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy. BMC Pharmacol Toxicol. 2016;17(1):44. doi:10.1186/s40360-016-0088-3.
32. Chapman LE, Darling AL, Brown JE. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab. 2016;42(5):316-327. doi:10.1016/j.diabet.2016.03.008.
33. Liu Q, Li S, Quan H, Li J. Vitamin B12 status in metformin treated patients: systematic review. Pietropaolo M, ed. PLoS One. 2014;9(6):e100379. doi:10.1371/journal.pone.0100379.
34. Ko S-H, Ko S-H, Ahn Y, et al. Association of Vitamin B 12 Deficiency and Metformin Use in Patients with Type 2 Diabetes. J Korean Med Sci. 2014;29(7):965. doi:10.3346/jkms.2014.29.7.965.
35. Wulffelé MG, Kooy A, Lehert P, et al. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. J Intern Med. 2003;254(5):455-463.
36. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010;340(may19 4):c2181-c2181. doi:10.1136/bmj.c2181.
37. Kang D, Yun J-S, Ko S-H, et al. Higher Prevalence of Metformin-Induced Vitamin B12 Deficiency in Sulfonylurea Combination Compared with Insulin Combination in Patients with Type 2 Diabetes: A Cross-Sectional Study. Wang Y, ed. PLoS One. 2014;9(10):e109878. doi:10.1371/journal.pone.0109878.
38. Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care. 2000;23(9):1227-1231. doi:10.2337/DIACARE.23.9.1227.
39. Yetley EA, Pfeiffer CM, Phinney KW, et al. Biomarkers of vitamin B-12 status in NHANES: a roundtable summary. Am J Clin Nutr. 2011;94(1):313S-321S. doi:10.3945/ajcn.111.013243.
40. Obeid R. Metformin Causing Vitamin B12 Deficiency: A Guilty Verdict Without Sufficient Evidence. Diabetes Care. 2014;37(2):e22-e23. doi:10.2337/dc13-2278.
41. Russo GT, Giandalia A, Romeo EL, et al. Diabetic neuropathy is not associated with homocysteine, folate, vitamin B12 levels, and MTHFR C677T mutation in type 2 diabetic outpatients taking metformin. J Endocrinol Invest. 2016;39(3):305-314. doi:10.1007/s40618-015-0365-9.
42. Chen S, Lansdown AJ, Moat SJ, et al. An observational study of the effect of metformin on B12 status and peripheral neuropathy. Br J Diabetes Vasc Dis. 2012;12(4):189-193. doi:10.1177/1474651412454924.
43. Reinstatler L, Qi YP, Williamson RS, Garn J V., Oakley GP. Association of Biochemical B12 Deficiency With Metformin Therapy and Vitamin B12 Supplements: The National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care. 2012;35(2):327-333. doi:10.2337/dc11-1582.
44. Salpeter SR, Greyber E, Pasternak GA, Salpeter (posthumous) EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. In: Salpeter SR, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2010:CD002967. doi:10.1002/14651858.CD002967.pub3.
45. Chang C-H, Sakaguchi M, Dolin P. Epidemiology of lactic acidosis in type 2 diabetes patients with metformin in Japan. Pharmacoepidemiol Drug Saf. 2016;25(10):1196-1203. doi:10.1002/pds.4030.
46. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Metformin, Sulfonylureas, or Other Antidiabetes Drugs and the Risk of Lactic Acidosis or Hypoglycemia: A nested case-control analysis. Diabetes Care. 2008;31(11):2086-2091. doi:10.2337/dc08-1171.
47. Malmberg K. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J. 2005;26(7):650-661. doi:10.1093/eurheartj/ehi199.
48. Lipska KJ, Bailey CJ, Inzucchi SE. Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency. Diabetes Care. 2011;34(6):1431-1437. doi:10.2337/dc10-2361.
49. FDA. Drug Safety and Availability - FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. [8 April 2016]. https://www.fda.gov/Drugs/DrugSafety/ucm493244.htm. Accessed March 14, 2017.

50. Amod A, Ascott-Evans BH, Berg GI, et al. The 2012 SEMDSA Guideline for the Management of Type 2 Diabetes (Revised). J Endocrinol Metab Diabetes South Africa. 2012;17(2):S1-S95.
51. Donnelly LA, Morris AD, Pearson ER. Adherence in patients transferred from immediate release metformin to a sustained release formulation: A population-based study. Diabetes, Obes Metab. 2009;11(4):338-342. doi:10.1111/j.1463-1326.2008.00973.x.
52. Levy J, Cobas RA, Gomes MB. Assessment of efficacy and tolerability of once-daily extended release metformin in patients with type 2 diabetes mellitus. Diabetol Metab Syndr. 2010;2(1):16. doi:10.1186/1758-5996-2-16.
53. Timmins P, Donahue S, Meeker J, Marathe P. Steady-state pharmacokinetics of a novel extended-release metformin formulation. Clin Pharmacokinet. 2005;44(7):721-729. doi:10.2165/00003088-200544070-00004.
54. Schwartz S, Fonseca V, Berner B, Cramer M, Chiang Y-K, Lewin A. Efficacy, Tolerability, and Safety of a Novel Once-Daily Extended-Release Metformin in Patients With Type 2 Diabetes. Diabetes Care. 2006;29(4):759-764. doi:10.2337/diacare.29.04.06.dc05-1967.
55. Fujioka K, Brazg RL, Raz I, et al. Efficacy, dose-response relationship and safety of once-daily extended-release metformin (Glucophage XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise: results from two double-blind, placebo-c. Diabetes Obes Metab. 2005;7(1):28-39. doi:10.1111/j.1463-1326.2004.00369.x.
56. Davidson J, Howlett H. New prolonged-release metformin improves gastrointestinal tolerability. Br J Diabetes Vasc Dis. 2004;4(4):273-277. doi:10.1177/14746514040040041101.
57. Feher MD, Al-Mrayat M, Brake J, Leong KS. Tolerability of prolonged-release metformin (Glucophage(R) SR) in individuals intolerant to standard metformin -- results from four UK centres. Br J Diabetes Vasc Dis. 2007;7(5):225-228. doi:10.1177/14746514070070050501.
58. Kim C-H, Han K-A, Oh H-J, et al. Safety, tolerability, and efficacy of metformin extended-release oral antidiabetic therapy in patients with type 2 diabetes: An observational trial in Asia. J Diabetes. 2012;4(4):395-406. doi:10.1111/j.1753-0407.2012.00220.x.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 9.2: Sulphonylureas

SEMDSA Type 2 Diabetes Guideline Expert Committee

Sulphonylureas (SUs) were first described in 1942 by the chemist Marcel Janbon when he observed that the sulphonamide antibiotics caused hypoglycaemia in animals.[1] Tolbutamide was developed in 1956 and glibenclamide in 1966. SUs have good glucose-lowering efficacy and safety, having been in clinical use for more than sixty years.[2]

9.2.1 Classification

SUs are traditionally classified as 1st or 2nd generation:

1st generation SUs include acetohexamide, tolbutamide, chlorpropamide, tolbutamide and tolazamide. Their use has been limited by side effects. Chlorpropamide is the only one still available in South Africa (Hypomide® and Diabitex®) but is no longer in use.

2nd generation SUs include glibenclamide, gliclazide (standard and modified-release), glipizide and glimepiride. These have a more nonpolar, lipophilic side chain, which results in a marked increase in their affinity for the SU receptor and hypoglycaemic potency (e.g. glibenclamide is 200 times more potent than tolbutamide).[3] All 2nd generation SUs are available in South Africa. There is no justification, pharmacological or otherwise, for classifying some SUs as 3rd generation.

Despite all SUs being classed together because of their chemistry and primary mode of action, it has become clear that these drugs are quite different in their effects. Controversies relating to specific agents have inappropriately been applied to the class as a whole. Note that glibenclamide is referred to as glyburide in the United States (US) and that gliclazide is not available in the US and some European countries. This has limited the number of trials where gliclazide is used as a comparator.

9.2.2 Gliclazide MR: The SU of choice

The 2012 SEMDSA guideline recommendation was that "glibenclamide therapy be phased out in favour of the other second generation SUs". The SEMDSA Guideline Expert Committee has considered all of the SU data and now strongly recommends that gliclazide modified-release should be the SU of choice at primary health care level. The reasons for this decision will be reviewed below.

9.2.3 Mode of action and pharmacology[2,4–9]

(This section contains optional supplementary reading)

All SUs are insulin secretagogues; they lower blood glucose through glucose-independent stimulation of insulin secretion from the pancreatic ß-cell.

They induce insulin release by binding to specific receptors on ATP-sensitive potassium (K_{ATP}) channels. K_{ATP} channels consist of two subunits, viz. a SU receptor (SUR) subunit and a pore forming subunit (Kir6.x). Each subunit has 2 isoforms (SUR1 & SUR2 and Kir6.1 & Kir6.2).

The SUR isoform in the pancreatic ß-cell is SUR1. The binding of SUs to SUR1 leads to closure of the potassium channel, prevents potassium efflux and results in membrane depolarization. This in turn leads to calcium influx, and the release of stored insulin from the ß-cell.[9]

Individual SUs differ in their affinity, specificity and binding to the SU receptor. Gliclazide, like glipizide and nateglinide, binds specifically and reversibly to pancreatic ß-cell SUR1 subunits at the A binding site. Glibenclamide and glimepiride bind SUR1 and SUR2 subunits (at both the A and B binding sites) irreversibly and non-specifically in a variety of tissues, including cardiac muscle.[4,5,10] Blocking the K_{ATP} channel on cardiac myocytes inhibits ischaemic pre-conditioning in animal models, and is a potential mechanism by which SUs may worsen cardiac outcomes.[11,12] The tissue distribution of K_{ATP} subunit isoforms and their interactions with second generation SUs is shown in Table I.

Tablel: Tissue distribution of SU receptors[4,5,10]

Tissue	SUR/Kir Isoform	Blocked by
Pancreatic ß-cell	SUR1A/Kir6.2 SUR1B/Kir6.2	All SUs and meglitinides Glibenclamide, glimepiride
Cardiac muscle	SUR2A/Kir6.2	Glibenclamide, glimepiride
Skeletal muscle	SUR2A/Kir6.2	Glibenclamide, glimepiride
Vascular smooth muscle	SUR2B/Kir6.1	Glibenclamide, glimepiride
Non-vascular smooth muscle	SUR2B/Kir6.2	Glibenclamide
Brain	SUR12B/Kir6.2	-

Gliclazide blocks SUR1A reversibly and this action is credited for its lower hypoglycaemic potential. Although glimepiride is non-specific in its interaction with the SUR subunit, it has a

lower affinity for the SUR than glibenclamide. This is believed to result in lower inhibition of K_{ATP} channels and less hypoglycaemic potential.[13,14]

Apart from K_{ATP} binding, all SUs except gliclazide also interact with exchange protein directly activated by cAMP (Epac2), which induces additional glucose-independent insulin exocytosis.[7]

The tissue specificity, reversible binding and lack of Epac2 interaction of gliclazide is credited chemically to its fewer hydrophobic domains and the lack of a benzamide moiety, and provides a pharmacological expectation for lower rates of hypoglycaemia and better cardiovascular (CV) safety.

The pharmacology of the second-generation SUs is summarised in Table II. Note that:

1. Glibenclamide and glimepiride have active metabolites with hypoglycaemic potential; gliclazide does not.
2. Despite similar metabolism and excretion to other SUs, glibenclamide has also been reported to accumulate in pancreatic ß-cells and to continue to stimulate insulin secretion during hypoglycaemia, leading to delayed recovery.[15,16]

9.2.5 Glycaemic efficacy

A 2014 Cochrane systematic review and meta-analysis of randomized clinical trials found no difference in the glycaemic efficacy of second generation SU monotherapy when compared with metformin monotherapy.[23]

A 2013 meta-analysis of SU monotherapy trials found a mean HbA1c reduction of -1.5% compared to placebo.[24] However this meta-analysis included 1st generation SUs, studies of short duration (three months or longer) and some trials had a very small number of participants. Other meta-analyses consistently show an approximate 1% reduction in HbA1c with second generation SUs when used as monotherapy or combination therapy with non-insulin agents.[25–28]

Two systematic reviews and meta-analyses of gliclazide studies demonstrated equivalent, if not slightly better, glycaemic efficacy compared with other SUs.[29,30]

The most recent network meta-analysis of comparative efficacies of glucose lowering drugs (GLDs) reports the following mean [95% CI] HbA1c reductions for SUs:[28]

As monotherapy (vs. placebo): -0.83 [-0.64 to -1.02]

As dual therapy: -1.25% [-0.76 to -1.72]

Table II: Comparison of second-generation SU drugs in available in South Africa

	Glibenclamide[17]	**Gliclazide[18]**	**Gliclazide-MR[18]**	**Glimepiride[19]**	**Glipizide[20]**
Chemical structure	Benzamide and sulphonyl moiety	Sulphonyl moiety only; fewer hydrophobic domains		Benzamide and sulphonyl moiety	Benzamide and sulphonyl moiety
ß-cell (SUR1)and cardiac (SUR2A selectivity	Non-selective	Selective for SUR1A; reversible binding		Non-selective	Selective for SUR1
Epac2 binding	Yes	No		Yes	Yes
Protein binding	99%	95%		>99%	>90%
Peak concentration (hours)	3-4	4-6	6 -12	2-3	1-3
Elimination half-life (hours)	10-16	10-12	16	5-8	2-4
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
Metabolites	2 active metabolites[21]	6 inactive metabolites		2 metabolites; 1 active	Inactive metabolites
Excretion of metabolites	50% renal 50% biliary	60-70% renal 10-20% biliary		60% renal 40% biliary	80% Kidney 20% biliary
Duration of action[2]	16-24 hours	10-24 hours	24 hours	16-24 hours	12-24 hours
Tablet size	5 mg	80 mg	30 & 60 mg	1, 2 & 4 mg	5 mg
Minimum daily dose	2.5 mg	40 mg	30 mg	1 mg	
Maximum dose	10 mg BD	160 mg BD	120 mg OD	8 mg OD	20 mg BD
Cheapest generic SEP* for maximum dose[22]	R35.00	R93.00	R123.00	R315.00	None available
Originator SEP* for maximum dose[22]	Euglucon® R426.00 Daonil® R572.00§	Diamicron® R177.00	Diamicron MR® R231.00	Amaryl® R938.00	Minidiab® R868.00

SUR=SU receptor; Epac= exchange protein directly activated by cAMP ; OD=once daily; BD= two times a day; SEP= single exit price; *Issued by Department of health and updated periodically as per South African regulations; for updated prices please consult The South African Medicines Price Registry. §Discontinued as at 2017

9.2.6 Hypoglycaemia

General

Inherent trial bias, publication bias, incomplete reporting and varying definitions of hypoglycaemia (less than 3.9, 3.5, 3.3, 3.1 and 2.8 mmol/L) hamper direct comparisons of the rates of hypoglycaemia across different randomised controlled trials (RCTs). Changing the cut point that defines hypoglycaemia can have a dramatic effect on results.[31]

Observational and epidemiological data have identified severe hypoglycaemia as a risk factor for poorer CV and mortality outcomes, though causality has not been proven.[32] The clinical significance of mild and moderate hypoglycaemia on clinical outcomes in type 2 diabetes is not known, but it is a predictor for severe hypoglycaemia and must therefore be avoided. Severe or major hypoglycaemia in a trial setting has usually been defined as blood glucose <2.8 mmol/L and/or hypoglycaemia that requires external assistance.

SUs are consistently associated with higher rates of any hypoglycaemia when compared with metformin monotherapy.[23,28] This is reflective of its mode of action as glucose-independent insulin secretagogues. Data from UKPDS showed that 17% of SU treated patients reported hypoglycaemia,[33] and over 10 years 1.4% to 2.5% of glibenclamide treated patients experienced at least one episode of severe hypoglycaemia per year.[34,35] A meta-analysis of SU RCTs revealed that 10% of users reported hypoglycaemia (<3.1 mmol/L).[36]

Hypoglycaemia data from RCTs can be misleading because they often exclude high-risk patients in favour of more highly motivated patients, and have more intensive monitoring. A more real-world systematic review and meta-analysis from population based studies showed that the for treatment regimens that included a SU, the prevalence of mild-to-moderate and severe hypoglycaemia was 30% and 5% respectively. The incidence was 200 mild-to-moderate events/100person-years and 1.0 severe event/100 person-years.[37]

Comparison of SUs.

Glibenclamide has been consistently associated with a higher hypoglycaemia risk among the second-generation SUs, particularly in older persons and in those with renal impairment.[38–42] This has led to its removal from the World Health Organisations Essential Medicines List.[43] The American Geriatrics Society's Beers Criteria lists a strong recommendation based on high quality evidence that glibenclamide be avoided in the elderly due to the potential risks.[44] In the meta-analysis by Gangji *et al*. the estimated increased relative risk for hypoglycaemia with glibenclamide versus other SUs was 1.83 [95% CI 1.35–2.49].[41]

Gliclazide and glimepiride has been reported to have an eight-fold lower hypoglycaemic risk than glibenclamide.[42,45] In a head-to-head comparison the European GUIDE study demonstrated that gliclazide modified-release also had lower rates of hypoglycaemia (BG < 3.0 mmol/l) than glimepiride with similar glycaemic efficacy. No episodes of severe hypoglycaemia were noted in this study.[46] Table III lists the estimated hypoglycaemic risk with second-generation SUs.[47]

Table III: Rates of severe hypoglycaemia with SUs (<2.8mmol/L)[47]

SU	Prevalence (proportion of patients)	Incidence (episodes/100-patient years)
Gliclazide	4.6%	0.86
Glipizide	8.0%	8.70
Glimepiride	11.5%	0.87
Glibenclamide	24%	16.00

Systematic reviews and meta-analyses that included gliclazide (including the modified-release formulation) compared to other SUs and oral glucose lowering drugs have confirmed that it has the lowest hypoglycaemic potential in its class, with equal if not better glycaemic efficacy.[29,30,36] However the number of severe hypoglycaemic events in these studies was extremely low with all therapies. The Schopman meta-analysis specifically examined hypoglycaemia outcomes and found that 10% of SU users experienced mild hypoglycaemia (defined as BG < 3.1 mmol/L) and 0.8% experienced severe hypoglycaemia (requiring external assistance). Gliclazide users had the lowest rate of mild and severe hypoglycaemia (1.4% and 0.1% respectively). Equivalent figures for glimepiride was 15.5 and 0.9% respectively.[36]

The ADVANCE study randomised 11 140 type 2 diabetes patients with high CV risk, a mean age of 66 years and disease duration of 8 years to either intensive treatment using a gliclazide modified-release strategy (75% used a dose of 120 mg daily) or conventional therapy.[70] The intensive treatment group achieved an HbA_{1c} of 6.5% over 5 years of follow-up. Despite this rather low glycaemic target for this population (by current standards), the rate of severe hypoglycaemia was 0.7 episodes/100 patients/year compared to 0.4 episodes/100 patients/year in the conventional treatment group whose mean HbA_{1c} was 7.3%. The proportion of patients who experienced any hypoglycaemic episode was 53% for intensive gliclazide modified-release based treatment vs. 38% for conventional therapy. We therefore recommend that even gliclazide modified-release, the SU with the lowest hypoglycaemic potential, be used with caution when the target HbA_{1c} is 6.5% or less.[70]

Factors that increase the risk of hypoglycaemia include exercise, increased age, presence of co–morbidities, hypoglycaemia unawareness, missed meals, excessive dieting or weight loss, alcohol, and diabetes duration and renal impairment.[36,48]

Multiple reports from a single study group using a single database (United Kingdom Clinical Practice Research Database – UKCPRD) have questioned the superior safety of gliclazide.[48–52] However, these are all observational studies, where gliclazide users are over-represented (80% of SU use is gliclazide), subjects are not matched, confounding by indication cannot be excluded, and residual confounding factors cannot be corrected for. Their data will need to be replicated in a controlled trial before being considered reliable.

9.2.7 Weight

In a systematic review and meta-analysis SU therapy was associated with a mean weight gain of 2.31 kg (95% CI 1.31- 3.32).[24] In the UKPDS the mean weight gain in patients assigned glibenclamide therapy was 1.7 kg over 10 years. In the ADVANCE study using gliclazide modified-release as the base therapy was not associated with weight gain.[70] The Landman *et al*.[30] meta-analysis of gliclazide RCTs demonstrated a 0.47kg mean weight gain when compared to controls.

9.2.8 Microvascular and macrovascular outcomes

9.2.8.1 Randomised controlled trials

In the UKPDS, intensive treatment with SUs (glibenclamide, chlorpropamide or glipizide) over 10 years in newly diagnosed diabetes resulted in a 0.9% HbA_{1c} difference and a 25% reduction of microvascular complications compared to standard treatment, where pharmacological intervention only occurred when the fasting plasma glucose exceeded 15 mmol/L.[34] In this RCT, these SUs had no macrovascular or mortality benefit compared to diet alone. This trial was designed to study the effect of intensive glycaemic control, and was not designed or powered to examine the safety of one drug class against another.[53]

The report of glibenclamide and chlorpropamide compared to metformin in obese patients (UKPDS 34 secondary analysis)[35] has been discussed in the section on metformin (see 9.1.3). It is not possible to determine definitively from this study whether the better results with metformin was due to a beneficial effect of metformin or a harmful effect of glibenclamide and

Table IV: Summary of meta-analyses of SUs and cardiovascular safety

Meta-analysis	Type and no. of studies included	SU vs. comparator	Outcome examined	Pooled point estimate [95%CI]§
Gangji *et al*., 2007[41]	RCT (21)	Glibenclamide vs secretagogues or insulin	CV events	0.84 [0.56–1.26]
Selvin *et al*., 2008[56]	RCT (5)	SU vs no SU	CV Mortality	0.92 [0.68 – 1.26]
	RCT (6)	SU vs no SU	All Cause Mortality	0.90 [1.10 – 1.85]
	RCT (5)	SU vs no SU	CV morbidity	0.89 [0.71 – 1.11]
Rao *et al*., 2008[62]	Observational (4)	SU+Met vs. diet, Met monotherapy, SU monotherapy	CV Mortality	1.29 [0.73 – 2.27]
	Observational (7)		All-cause mortality	1.19 [0.88 – 1.62]
	Observational (5)		CV mortality and hospitalisation	***1.43 [1.10 – 1.85]***
Phung *et al*., 2013[57]	Observational (9)	SU vs no SU	CV Mortality	***1.27 [1.18 – 1.34]***
	RCT (7)	SU vs no SU	CV Mortality	1.22 [0.63 – 2.39]
Monami *et al*., 2013[60]	RCT (30)	SU vs no SU	MACE	1.08 [0.86 – 1.36]
	RCT (37)	SU vs no SU	All-cause mortality	***1.22 [1.01 – 1.49]***
Hemmingsen *et al*., 2013[23]	RCT (3)	SU monotherapy vs Met	CV Mortality	1.47 [0.54 – 4.01]
	RCT (6)	SU monotherapy vs Met	All-cause mortality	0.98 [0.61 – 1.58]
	RCT (6)	SU monotherapy vs Met	CV Morbidity	**0.67 [0.48 – 0.93]**
Forst *et al*., 2013[63]	Observational (4)	SU vs no SU	CV Mortality	***2.72 [1.95 – 3.79]***
	Observational (12)	SU vs no SU	All-cause mortality	***1.92 [1.48 – 2.49]***
Zhang *et al*., 2014[61]	RCT (4)	DPP-4i vs SU	CV events	**0.53 [0.32 – 0.87]**
Simpson *et al*., 2015[58]	RCT (7) Observational (7)	Glipizide vs glibenclamide	CV Mortality	1.01 [0.72 – 1.43]
			All Cause Mortality	0.98 [0.80 – 1.19]
		Glimepiride vs glibenclamide	CV Mortality	0.79 [0.57 – 1.11]
			All Cause Mortality	***0.83 [0.68 – 1.00]***
		Gliclazide vs glibenclamide	CV Mortality	***0.60 [0.45 – 0.84]***
			All Cause Mortality	***0.65 [0.53 – 0.79]***
Rados *et al*., 2016[59]	RCT (37)	SU vs no SU	All Cause Mortality	1.12 [0.96 - 1.30]
	RCT (37)		CV Mortality	1.12 [0.87 - 1.42]
	RCT (23)		Myocardial infarction	0.92 [0.76 - 1.12]
	RCT (23)		Stroke	1.16 [0.81 - 1.66]
Palmer *et al*.,2016[28]	RCT (25)	SU monotherapy vs Met*	CV Mortality	1.25 [0.59 - 2.67]
			All-cause mortality	1.19 [0.81 - 1.75]
	RCT (26)	Dual therapy: Met + SU vs Met + non-SU**	CV Mortality	1.00 Reference
			All-cause mortality	1.00 Reference

SU=SU; CI=confidence interval; RCT= randomised controlled trial; CV=cardiovascular; Met=metformin
§95% Values <1.00 favour SU safety; Confidence Interval: statistically significant if the interval does not cross 1.00 (bold italics)
*Other monotherapies (TZD, DPP-4i, SGLT2i, AGI, meglitinides and placebo vs metformin were not significantly different to SU vs metformin).
**For 2nd line therapy, metformin + SU was used as reference; metformin + any one of TZD, DPP-4i, SGLT2i, GLP-1RA, meglitinides and placebo was not significantly different to the Met + SU combination

chlorpropamide (the argument being that the benefits of HbA_{1c} reduction on macrovascular disease and mortality with these SUs may have been negated by the harmful effects of these drugs). This has added to the speculation from the University Group Diabetes Program (UGDP), which reported (controversially) a higher CV mortality with tolbutamide, that SUs as a class have harmful CV effects.[54]

The ADVANCE study, using a gliclazide modified-release strategy, demonstrated a significant reduction in microvascular outcomes (and therefore also the combined microvascular and macrovascular outcomes), driven mainly by the reduction in the incidence of nephropathy.[70] Another study indicated potential renal risks for elderly patients using glimepiride versus gliclazide.[39]

Rosenstock *et al*. reviewed 15 published RCTs that were of ≥72- week duration and included SU therapy versus an active comparator (incl. metformin, DPP-4i, GLP-1RA, TZD and insulin) or as part of a treatment strategy.[55] None of them reported an increased CV risk with SU use. However, some of the studies (e.g. UKPDS and ADVANCE) studied the effect of intensive control vs. less intensive control, and were not designed or powered to demonstrate safety of SUs against other therapies, so that any benefit (or lack of harm) might be credited to improved glycaemic control rather than the SU. In the studies that did target equivalent glycaemic control, none of them were powered to demonstrate CV safety, and there was inconsistency in CV event reporting and adjudication.

More formal systematic reviews and meta-analyses of RCTs examining the CV risk/safety of SUs have also generally not demonstrated an increased or reduced CV risk with second generation SUs[23,28,41,56–59] (Table IV). One meta-analysis showed an increase in all-cause mortality,[60] one showed a reduction in non-fatal CV events,[23] and one showed a lower CV risk lower with DPP-4-inhibitors compared to SUs.[61] However they suffer the same weaknesses of the underlying RCTs analysed (design flaws, inadequate follow-up, selection-bias, inconsistent reporting of CV events, varying definitions and event adjudication, publication bias), and the heterogeneity in these analyses has generally been quite high, thus reducing their reliability.[12]

Observational Studies

Observational studies have the advantage of representing more "real-world" population data rather than the highly selected populations of industry-sponsored drug trials. Abdelmoneim *et al*. has listed the 68 published observational studies on SU use and CV outcomes to January 2015 in a supplementary table.[12] Table IV summarises the meta-analyses of these observational studies, which, in contrast to extrapolated RCT data, mostly suggest an increased CV and mortality risk (up to 379%) with SU use.[57,62,63] Abdelmoneim *et al*. discusses the inherent weaknesses of observational studies particularly in relation to SUs and CV outcomes.[12]

Data from observational studies can never be used as proof of causality; it merely generates a hypothesis that then needs to be proven in a suitably designed RCT. In the absence of such suitably designed trials, the strong signal from these observational studies cannot be ignored. One of the additional weaknesses of studies examining SUs and CV risk is that the SUs are often examined as a homogeneous class when in fact their pharmacology does differ. It is reassuring then, that the observational studies that report CV risk with different SUs have consistently reported better outcomes with gliclazide when compared to other SUs.[64–68] The better CV safety of gliclazide has been confirmed in the meta-analysis by Simpson *et al*.[58]

In summary, the inherent weaknesses of both the meta-analyses of RCTs not designed to investigate the CV safety of SUs, and the weaknesses of observational studies means that there is no definitive answer as to the CV safety or risk of SUs as a class. The ongoing CAROLINA trial is comparing linagliptin and glimepiride in a dedicated CV safety design and will hopefully lend more clarity to this issue.[55] In the meantime the balance of probabilities must rest with RCTs, which favour CV safety. The ADVANCE study rather than UKPDS more closely resembles the day-to-day use of SUs (as add-on therapy), and this trial did not show evidence of CV harm.[70] Even if the observational data on higher CV risk with SUs are true, from a meta-analysis the same data the risk with gliclazide is lower than glibenclamide and glimepiride, and not different to metformin.

9.2.9 Pleiotropic effects and non-glycaemic benefits

Gliclazide has been shown to have additional pleiotropic effects:[18]

1. Extra-pancreatic effects on glucose metabolism
    a. Increase peripheral insulin sensitivity and increases muscle glucose uptake by +35%, due to its effect on muscle glycogen synthetase and a post-transcriptional action on GLUT4 glucose carriers.
    b. Decreases hepatic glucose production, leading to an improvement in fasting blood glucose levels
2. Haemovascular effects: Gliclazide decreases microthrombosis by two mechanisms which may be involved in complications of diabetes:
    a. A partial inhibition of platelet aggregation and adhesion
    b. A restoration of the vascular endothelium fibrinolytic activity with an increase in t-PA activity.
    c. Antioxidant effects: A controlled clinical study in diabetics has confirmed the antioxidant effects of gliclazide i.e. a reduction in plasma levels of lipid peroxides and an increase in the activity of erythrocyte superoxide dismutase.
3. Cancers: Data about an increased cancer risk with SUs and insulin are unclear. Nevertheless, the cancer risk with gliclazide has been shown to be lower than insulin and other SUs.[2,8]

9.2.10 The choice of SU

SUs are one of the more effective glucose lowering drugs that can improve glycaemic control rapidly. They are relatively inexpensive, have a long history of clinical use, and are relatively

simple to use. Their clinical use predates the US Food and Drug Administration (FDA) regulatory requirement for proven CV safety,[69] and there are no suitably designed trials that have examined this issue specifically. What we do know for now, is that there is at least some data to suggest that SUs may increase CV risk, and that there is a plausible mechanism by which this might occur (hypoglycaemia and SUR binding on cardiac myocyes). How then, can we best manage this potential risk? Firstly, we should use the SU with the lowest risk for hypoglycaemia. Secondly, we should favour SUs with proven outcomes and the best evidence for CV safety, especially when combined with metformin. Thirdly, a SU with the best renal safety is highly preferable to minimise inappropriate prescribing and dosing, particularly at primary care level. Fourthly, we should prefer, at least on theoretical grounds, a SU that does not interact with cardiac myocytes. Additional considerations would be potential non-glycaemic benefits, once daily dosing to improve compliance and adherence, and availability of cost-effective generic medicines.

Based on our review of the SU data, we make the following observations:

1. Gliclazide and its modified-release formulation has demonstrated the lowest hypoglycaemic potential in the SU class, in head-to-head RCTs,[46] meta-analyses[29,30,36] and observational studies.[45] The rate of severe hypoglycaemia with gliclazide is very low (estimated at 0.1%).
2. The WHO has concluded that the adverse safety profile of glibenclamide, especially in older patients, warranted it being replaced by gliclazide on the WHO Essential Medicines List.[43] The The American Geriatrics Society makes a strong recommendation based on strong evidence that glibenclamide is unsafe and must not be used in older patients.[44]
3. A gliclazide modified-release based intensive treatment strategy has proven microvascular benefit and macrovascular safety in a long term RCT that included older type 2 diabetes patients, patients at high CV risk, and those taking concomitant metformin therapy.[70] Glimepiride may have adverse renal outcomes in some sub-populations of type 2 diabetes patients.[39]
4. In observational studies and meta-analyses of SU-related CV safety, gliclazide has been shown to have a better safety profile than glibenclamide and glimepiride.[64–68]
5. There has been no evidence of an adverse safety signal with a gliclazide-metformin combination (as exists for glibenclamide).[35]
6. The gliclazide dose does not require adjustment in CKD and can be used even in stage 5 CKD; glimepiride either should not be used or will need dose adjustments in Stage 3 CKD or worse; glibenclamide must not be used in stage 3 CKD or worse.[71–73] *(vide infra)*
7. Gliclazide and its modified-release formulation do not bind SUR2 on cardiac myocytes; this potentially harmful interaction therefore does not exist for gliclazide[2,4–9] (and possibly explains it better CV safety).
8. Gliclazide and its modified-release formulation have beneficial pleiotropic effects, not all of which are shared by the other SUs.
9. Gliclazide MR is dosed once daily, reduces the pill burden and can improve adherence and compliance with therapy.
10. Gliclazide MR is available in South Africa as cost-effective generic tablets. In the private health sector gliclazide MR is significantly less expensive than generic glimepiride tablets or glipizide. Using the most inexpensive formulations available at maximum recommended doses, glimepiride is currently 256% more expensive, while glipizide is 933% more expensive than gliclazide modified-release (Table II).[22]

Based on these observations we *strongly recommend* that gliclazide MR should be the SU of choice at primary care level and that glibenclamide *must* not be used at primary health care level.

9.2.10 Indications for use

SEMDSA recommends that gliclazide modified-release be considered for use only when the target HbA_{1c} is greater than 6.5% in the following situations:

1. As monotherapy (first-line)
   a. In patients who have intolerable side-effects with metformin and its extended-release formulation, or when metformin is contraindicated.
   b. In patients with symptoms attributable to hyperglycaemia when rapid symptom control is desirable (these patients will often need initial dual therapy with metformin and gliclazide modified-release).
   c. In non-obese patients gliclazide modified-release is an acceptable alternative first-line therapy.
2. As add on (second-line) to metformin or other initial drug therapy in patients not achieving or maintaining their glycaemic targets.
3. As a third glucose lowering drug in patients not achieving or maintaining their glycaemic targets on a two drug regimen that does not already include a SU.

9.2.10 Dosing and prescribing

Dosing

1. The usual starting dose for gliclazide modified-release is 30 to 60 mg administered once daily with the morning meal. Consider starting with the higher dose when the HbA_{1c} target is >0.5% from the patient's prevailing HbA_{1c} level.
2. The dose can be escalated by 30 to 60 mg every 1 to 4 weeks, guided by fasting glucose levels.
3. The maximum dose is 120 mg administered once daily with the morning meal.
4. The 60 mg tablets are scored and can be broken to improve cost effectiveness.

Prescribing in chronic kidney disease

Glibenclamide and glimepiride have active metabolites that accumulate when renal function is impaired. Gliclazide and glipizide do not have active metabolites. The most recent

Table V: Renal dose adjustments for SUs[71–73]

CKD Stage / eGFR (ml/min/1.73m²)	Stage 1-2 ≥ 60	Stage 3A and B 30-59	Stage 4 15-29	Stage 5 <15	5D On dialysis
Glibenclamide	Normal dose	Must not use			
Glimepiride§	Normal dose	Caution – 1mg	Reduce – 1mg	1mg / Do not use	Do not use
Glipizide	Normal dose	No dose adjustment			
Gliclazide / MR	Normal dose	No dose adjustment			

§Differing recommendations for glimepiride:
Reference 57 (KDOQI): Glipizide is the preferred SU (gliclazide is not available in USA); if using glimepiride, recommended dose is 1mg for stage 3-5; not recommended for stage 5D
Reference 58 (Hahr): Stage 3 – use with caution; Stage 4&5 – avoid use
Reference 59 (Arnouts): Stage 3&4 – reduce dose to 1mg; Stage 5 – do not use

guidelines on SU dose adjustments in renal disease are summarised in Table V.[71–73]

Special precautions and side effects

1. Hypoglycaemia
   a. Use with caution when the target HbA_{1c} is ≤ 6.5% as the risk of hypoglycaemia may be unacceptably high.
   b. If mild hypoglycaemia occurs unexpectedly (e.g. not due to unplanned missed meals or unplanned exercise), reduce the dose by 30 to 60 mg.
   c. A single episode of severe hypoglycaemia or recurrent episodes of mild hypoglycaemia would be a strong indication to switch to an alternative glucose lowering drug.
2. Although renal dose adjustments may not be necessary with gliclazide modified-release, caution is still advised especially when the eGFR is < 30 ml/min/1.73m². In any case, these patients must be managed at specialist care level, and not at primary care level.
3. Serious adverse drug reactions include pancytopenia, thrombocytopenia, hepatitis, cholestatic jaundice, pyrexia, pancreatitis and skin reactions. These are very rare
4. A history of allergy to sulphonamide antibiotics is not a contraindication to gliclazide modified-release use as the cross-reactivity is low.[74]
5. All SUs are contra-indicated in advanced liver disease because of their hepatic metabolism and biliary excretion.

Authors: Aslam Amod and Fraser J Pirie
Editors: Zaheer Bayat, Ankia Coetzee, Nazeer A Mohamed, Joel A Dave, Tanya E Kinvig

References

1. Janbon M, Chaptal J, Vedel A, Schaap J (1942). [Accidents hypoglycémiques graves par un sulfamidothiodiazol (le VK 57 ou 2254 RP]. Montpellier Med. 441: 21–22.
2. Thulé PM, Umpierrez G. Sulfonylureas: A New Look at Old Therapy. Curr Diab Rep. 2014;14(4):473. doi:10.1007/s11892-014-0473-5.
3. Skillman TG, Feldman JM. The pharmacology of sulfonylureas. Am J Med. 1981;70(2):361-372.
4. Ashcroft FM. ATP-sensitive potassium channelopathies: focus on insulin secretion. J Clin Invest. 2005;115(8):2047-2058. doi:10.1172/JCI25495.
5. Ashcroft FM, Gribble FM. Tissue-specific effects of sulfonylureas: lessons from studies of cloned K(ATP) channels. J Diabetes Complications. 2000;14(4):192-196.
6. Gribble FM, Reimann F. Differential selectivity of insulin secretagogues: mechanisms, clinical implications, and drug interactions. J Diabetes Complications. 2003;17(2 Suppl):11-15.
7. Seino S, Zhang C-L, Shibasaki T. Sulfonylurea action re-revisited. J Diabetes Investig. 2010;1(1-2):37-39. doi:10.1111/j.2040-1124.2010.00014.x.
8. Sola D, Rossi L, Schianca GPC, et al. State of the art paper Sulfonylureas and their use in clinical practice. Arch Med Sci. 2015;4(4):840-848. doi:10.5114/aoms.2015.53304.
9. Bennett K, James C, Hussain K. Pancreatic β-cell KATP channels: Hypoglycaemia and hyperglycaemia. Rev Endocr Metab Disord. 2010;11(3):157-163. doi:10.1007/s11154-010-9144-2.
10. Abdelmoneim AS, Hasenbank SE, Seubert JM, Brocks DR, Light PE, Simpson SH. Variations in tissue selectivity amongst insulin secretagogues: a systematic review. Diabetes, Obes Metab. 2012;14(2):130-138. doi:10.1111/j.1463-1326.2011.01496.x.
11. Gore MO, McGuire DK. Resolving drug effects from class effects among drugs for type 2 diabetes mellitus: more support for cardiovascular outcome assessments. Eur Heart J. 2011;32(15):1832-1834. doi:10.1093/eurheartj/ehr019.
12. Abdelmoneim AS, Eurich DT, Light PE, et al. Cardiovascular safety of sulphonylureas: over 40 years of continuous controversy without an answer. Diabetes, Obes Metab. 2015;17(6):523-532. doi:10.1111/dom.12456.
13. Briscoe VJ, Griffith ML, Davis SN. The role of glimepiride in the treatment of type 2 diabetes mellitus. Expert Opin Drug Metab Toxicol. 2010;6(2):225-235. doi:10.1517/17425250903512955.
14. Müller G, Hartz D, Pünter J, Okonomopulos R, Kramer W. Differential interaction of glimepiride and glibenclamide with the beta-cell sulfonylurea receptor. I. Binding characteristics. Biochim Biophys Acta. 1994;1191(2):267-277.
15. Hellman B, Sehlin J, Täljedal IB. Glibenclamide is exceptional among hypoglycaemic sulphonylureas in accumulating progressively in beta-cell-rich pancreatic islets. Acta Endocrinol (Copenh). 1984;105(3):385-390.
16. Szoke E, Gosmanov NR, Sinkin JC, et al. Effects of glimepiride and glyburide on glucose counterregulation and recovery from hypoglycemia. Metabolism. 2006;55(1):78-83. doi:10.1016/j.metabol.2005.07.009.
17. Diabeta® (glibenclamide tablets) [product monograph]: Quebec, Canada, sanofi-aventis Canada Inc.; November 2016. http://products.sanofi.ca/en/diabeta.pdf. Accessed March 20, 2017.
18. Diamicron® (gliclazide tablets) [product monograph]: Quebec, Canada, SERVIER CANADA Inc.; July 2016. www.servier.ca/sites/default/files/webform/products/EN - Diamicron 80 PM July 13%2C 2016.pdf?ts=1490027803. Accessed March 20, 2017.
19. Amaryl® (glimepiride tablets) [product monograph]: Quebec, Canada, sanofi-aventis Canada Inc.; September 2013.
20. Glucotrol® (glipizide tablets) [package insert]: New York, NY, USA. Pfizer Inc.; October 2016. http://labeling.pfizer.com/ShowLabeling.aspx?id=579. Accessed March 20, 2017.
21. Rydberg T, Jönsson A, Karlsson MO, Melander A. Concentration-effect relations of glibenclamide and its active metabolites in man: modelling of pharmacokinetics and pharmacodynamics. Br J Clin Pharmacol. 1997;43(4):373-381.
22. South African Medicine Price Registery. Database Of Medicine Prices 14th March 2017. http://www.mpr.gov.za/Publish/ViewDocument.aspx?DocumentPublicationId=3285. Accessed March 20, 2017.
23. Hemmingsen B, Schroll JB, Wetterslev J, et al. Sulfonylurea versus metformin monotherapy in patients with type 2 diabetes: a Cochrane systematic review and meta-analysis of randomized clinical trials and trial sequential analysis. C Open. 2014;2(3):E162-E175. doi:10.9778/cmajo.20130073.

24. Hirst JA, Farmer AJ, Dyar A, Lung TWC, Stevens RJ. Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis. Diabetologia. 2013;56(5):973-984. doi:10.1007/s00125-013-2856-6.
25. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The Effect of Oral Antidiabetic Agents on A1C Levels: A systematic review and meta-analysis. Diabetes Care. 2010;33(8):1859-1864. doi:10.2337/dc09-1727.
26. Bennett WL, Maruthur NM, Singh S, et al. Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations. Ann Intern Med. 2011;154(9):602. doi:10.7326/0003-4819-154-9-201105030-00336.
27. Liu S-C, Tu Y-K, Chien M-N, Chien K-L. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. Diabetes, Obes Metab. 2012;14(9):810-820. doi:10.1111/j.1463-1326.2012.01606.x.
28. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes. JAMA. 2016;316(3):313. doi:10.1001/jama.2016.9400.
29. Chan SP, Colagiuri S. Systematic review and meta-analysis of the efficacy and hypoglycemic safety of gliclazide versus other insulinotropic agents. Diabetes Res Clin Pract. 2015;110(1):75-81. doi:10.1016/j.diabres.2015.07.002.
30. Landman GWD, de Bock GH, van Hateren KJJ, et al. Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Trials. Letizia Hribal M, ed. PLoS One. 2014;9(2):e82880. doi:10.1371/journal.pone.0082880.
31. Swinnen SGHA, Mullins P, Miller M, Hoekstra JBL, Holleman F. Changing the glucose cut-off values that define hypoglycaemia has a major effect on reported frequencies of hypoglycaemia. Diabetologia. 2009;52(1):38-41. doi:10.1007/s00125-008-1147-0.
32. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology. Diabetes Care. 2009;32(1):187-192. doi:10.2337/dc08-9026.
33. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. Diabetes. 1995;44(11):1249-1258.
34. Turner R. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-853. doi:10.1016/S0140-6736(98)07019-6.
35. Turner R. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352(9131):854-865. doi:10.1016/S0140-6736(98)07037-8.
36. Schopman JE, Simon ACR, Hoefnagel SJM, Hoekstra JBL, Scholten RJPM, Holleman F. The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2014;30(1):11-22. doi:10.1002/dmrr.2470.
37. Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and Incidence of Hypoglycaemia in 532,542 People with Type 2 Diabetes on Oral Therapies and Insulin: A Systematic Review and Meta-Analysis of Population Based Studies. Barengo NC, ed. PLoS One. 2015;10(6):e0126427. doi:10.1371/journal.pone.0126427.
38. Chahal H. Comparative Safety and Efficacy of Glibenclamide in the Elderly. 19th Expert Comm Sel Use Essent Med. 2013:1-32.
39. Glyburide, Gliclazide or Glimepiride for Elderly Patients with Type 2 Diabetes: A Review of the Clinical Effectiveness and Safety – An Update [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Aug 18. https://www.ncbi.nlm.nih.gov/books/NBK315876/. Accessed March 20, 2017.
40. Andersen SE, Christensen M. Hypoglycaemia when adding sulphonylurea to metformin: a systematic review and network meta-analysis. Br J Clin Pharmacol. 2016;82(5):1291-1302. doi:10.1111/bcp.13059.
41. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A Systematic Review and Meta-Analysis of Hypoglycemia and Cardiovascular Events: A comparison of glyburide with other secretagogues and with insulin. Diabetes Care. 2007;30(2):389-394. doi:10.2337/dc06-1789.
42. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. Diabetes Metab Res Rev. 17(6):467-473.
43. WHO Model List of Essential Medicines (19th List amended Nov 2015). http://www.who.int/medicines/publications/essentialmedicines/en/. Published August 2015. Accessed October 30, 2016.
44. American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2012;60(4):616-631. doi:10.1111/j.1532-5415.2012.03923.x.
45. Clemens KK, McArthur E, Dixon SN, Fleet JL, Hramiak I, Garg AX. The Hypoglycemic Risk of Glyburide (Glibenclamide) Compared with Modified-Release Gliclazide. Can J Diabetes. 2015;39(4):308-316. doi:10.1016/j.jcjd.2015.01.001.
46. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest. 2004;34(8):535-542. doi:10.1111/j.1365-2362.2004.01381.x.
47. Tayek J. SUR receptor activity vs. incidence of hypoglycaemia and cardiovascular mortality with sulphonylurea therapy for diabetics. Diabetes, Obes Metab. 2008;10(11):1128-1129. doi:10.1111/j.1463-1326.2008.00928.x.
48. van Dalem J, Brouwers MCGJ, Stehouwer CDA, et al. Risk of hypoglycaemia in users of sulphonylureas compared with metformin in relation to renal function and sulphonylurea metabolite group: population based cohort study. BMJ. 2016;354354:i3625. doi:10.1136/bmj.i3625.
49. Morgan CL, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Association between first-line monotherapy with sulphonylurea versus metformin and risk of all-cause mortality and cardiovascular events: a retrospective, observational study. Diabetes, Obes Metab. 2014;16(10):957-962. doi:10.1111/dom.12302.
50. Bannister C a, Holden SE, Jenkins-Jones S, et al. Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls. Diabetes, Obes Metab. 2014;16(11):1165-1173. doi:10.1111/dom.12354.
51. Gamble J-M, Thomas JM, Twells LK, Midodzi WK, Majumdar SR. Comparative effectiveness of incretin-based therapies and the risk of death and cardiovascular events in 38,233 metformin monotherapy users. Medicine (Baltimore). 2016;95(26):e3995. doi:10.1097/MD.0000000000003995.
52. Morgan CL, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality. Diabetes, Obes Metab. 2014;16(10):977-983. doi:10.1111/dom.12306.
53. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. Diabetologia. 1991;34(12):877-890.
54. Leibel B. An analysis of the University Group Diabetes Study Program: data results and conclusions. Can Med Assoc J. 1971;105(3):292-294.
55. Rosenstock J, Marx N, Kahn SE, et al. Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. Diab Vasc Dis Res. 2013;10(4):289-301. doi:10.1177/1479164112475102.
56. Selvin E, Bolen S, Yeh H-C, et al. Cardiovascular Outcomes in Trials of Oral Diabetes Medications. Arch Intern Med. 2008;168(19):2070. doi:10.1001/archinte.168.19.2070.
57. Phung OJ, Schwartzman E, Allen RW, Engel SS, Rajpathak SN. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. Diabet Med. 2013;30(10):1160-1171. doi:10.1111/dme.12232.
58. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. Lancet Diabetes Endocrinol. 2015;3(1):43-51. doi:10.1016/S2213-8587(14)70213-X.
59. Rados DV, Pinto LC, Remonti LR, Leitão CB, Gross JL. The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials. Lehman R, ed. PLOS Med. 2016;13(4):e1001992. doi:10.1371/journal.pmed.1001992.
60. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes, Obes Metab. 2013;15(10):938-953. doi:10.1111/dom.12116.
61. Zhang Y, Hong J, Chi J, Gu W, Ning G, Wang W. Head-to-head comparison of dipeptidyl peptidase-IV inhibitors and sulfonylureas - a meta-analysis from randomized clinical trials. Diabetes Metab Res Rev. 2014;30(3):241-256. doi:10.1002/dmrr.2482.
62. Rao AD, Kuhadiya N, Reynolds K, Fonseca V a. Is the Combination of Sulfonylureas and Metformin Associated With an Increased Risk of

Cardiovascular Disease or All-Cause Mortality?: A meta-analysis of observational studies. Diabetes Care. 2008;31(8):1672-1678. doi:10.2337/dc08-0167.

63. Forst T, Hanefeld M, Jacob S, et al. Association of sulphonylurea treatment with all-cause and cardiovascular mortality: A systematic review and meta-analysis of observational studies. Diabetes Vasc Dis Res. 2013;10(4):302-314. doi:10.1177/1479164112465442.
64. Sadikot SM, Mogensen CE. Risk of coronary artery disease associated with initial sulphonylurea treatment of patients with type 2 diabetes: A matched case–control study. Diabetes Res Clin Pract. 2008;82(3):391-395. doi:10.1016/j.diabres.2008.09.004.
65. Khalangot M, Tronko M, Kravchenko V, Kovtun V. Glibenclamide-related excess in total and cardiovascular mortality risks: Data from large Ukrainian observational cohort study. Diabetes Res Clin Pract. 2009;86(3):247-253. doi:10.1016/j.diabres.2009.09.008.
66. Zeller M, Danchin N, Simon D, et al. Impact of Type of Preadmission Sulfonylureas on Mortality and Cardiovascular Outcomes in Diabetic Patients with Acute Myocardial Infarction. J Clin Endocrinol Metab. 2010;95(11):4993-5002. doi:10.1210/jc.2010-0449.
67. Jørgensen CH, Gislason GH, Andersson C, et al. Effects of oral glucose-lowering drugs on long term outcomes in patients with diabetes mellitus following myocardial infarction not treated with emergent percutaneous coronary intervention - a retrospective nationwide cohort study. Cardiovasc Diabetol. 2010;9(1):54. doi:10.1186/1475-2840-9-54.
68. Schramm TK, Gislason GH, Vaag A, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011;32(15):1900-1908. doi:10.1093/eurheartj/ehr077.
69. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry. Diabetes mellitus – evaluating cardiovascular risk in new antidiabetes therapies to treat type 2 diabetes. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ ucm071627.pdf. Published 2008. Accessed February 25, 2016.
70. Patel A, MacMahon S, Chalmers J, et al. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2008;358(24):2560-2572. doi:10.1056/NEJMoa0802987.
71. Rocco M V., Berns JS. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis. 2012;60(5):850-886. doi:10.1053/j.ajkd.2012.07.005.
72. Arnouts P, Bolignano D, Nistor I, et al. Glucose-lowering drugs in patients with chronic kidney disease: a narrative review on pharmacokinetic properties. Nephrol Dial Transplant. 2014;29(7):1284-1300. doi:10.1093/ndt/gft462.
73. Hahr AJ, Molitch ME. Management of diabetes mellitus in patients with chronic kidney disease. Clin Diabetes Endocrinol. 2015;1(1):2. doi:10.1186/s40842-015-0001-9.
74. Strom BL, Schinnar R, Apter AJ, et al. Absence of Cross-Reactivity between Sulfonamide Antibiotics and Sulfonamide Nonantibiotics. N Engl J Med. 2003;349(17):1628-1635. doi:10.1056/NEJMoa022963.
75. Lee Y -h., Lee CJ, Lee HS, et al. Comparing kidney outcomes in type 2 diabetes treated with different sulphonylureas in real-life clinical practice. Diabetes Metab. 2015;41(3):208-215. doi:10.1016/j.diabet.2015.01.004.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 9.3: Drug review - Pioglitazone

SEMDSA Type 2 Diabetes Guideline Expert Committee

9.3.1 History

The thiazolidinediones are also known as TZDs or glitazones. The prototypical TZD was ciglitazone developed in the early 1980's but this drug was never marketed.

Troglitazone was the first TZD to be approved for clinical use by the US Food and Drug Administration (FDA) in 1997 despite its potential liver toxicity. The drug was embarrassingly withdrawn by the FDA in 2000 because of idiosyncratic and often fatal hepatotoxicity.[1]

Rosiglitazone was released in 1999 and was popular in the US until a meta-analysis reported its association with a higher risk of myocardial infarction and possibly cardiovascular mortality.[2] The European Medicines Agency recommended the suspension of rosiglitazone in 2010, at which time the drug was also withdrawn from the UK and India. The Medicines Control Council resolved to withdraw rosiglitazone from the South African market on 03 June 2011.[3] The FDA responded in 2010 by imposing sales and distribution restrictions on rosiglitazone and ordered an independent analysis of the RECORD trial[4] results. The Duke Clinical Research Institute conducted this analysis and found no statistical difference in cardiovascular outcomes with rosiglitazone versus a sulphonylurea when combined with metformin. These re-adjudicated results could not dismiss an increased risk of heart attack with rosiglitazone versus placebo, because the trial did not use a placebo. The FDA has since lifted the distribution restrictions on rosiglitazone in the US, with a "black-box" label warning that the data on the risks of myocardial ischaemia remain inconclusive.[5] The decision to lift restrictions has been supported subsequently by a post hoc analysis of the BARI 2D trial, in which 992 subjects on rosiglitazone had no significant change in the rate of myocardial infarction, with a trend toward benefit, as well as a 64% reduction in the risk of stroke and a 28% reduction in the risk of the composite cardiovascular endpoint (death, MI and stroke).[6] A review of some of the observational data used in the meta-analyses that discredited rosiglitazone have been shown to have important deficiencies. Nevertheless, it is unlikely that rosiglitazone will regain popularity, as it offers no unique advantages over pioglitazone.

Pioglitazone was also released in 1999 and has an equally chequered history albeit for different reasons. It is the only TZD available in South Africa. The 2012 SEMDSA guideline did not include pioglitazone in the treatment algorithm mainly because of unresolved concerns regarding bladder cancers.[7] This information has been updated and reviewed, and the current evidence favours overall benefit over risk. Pioglitazone is therefore included as a treatment option in the current guideline.

9.2.2 Mode of action and pharmacology

Pioglitazone acts via activation of specific nuclear receptors called peroxisome proliferator activated receptor-gamma (PPARγ). This PPARγ agonist activity leads to increased transcription of proteins, which augment the post-receptor actions of insulin mainly fat cells (which are rich in PPARγ nuclear receptors) but also in liver and skeletal muscle cells. Pioglitazone is therefore a true insulin-sensitiser. It reduces hyperinsulinaemia and improves pancreatic ß-cell function. Treatment with pioglitazone has been shown to reduce hepatic glucose output and to increase peripheral glucose disposal in the presence of insulin resistance.[8]

Pioglitazone is rapidly absorbed after oral administration and absorption is not influenced by food. It reaches peak plasma concentrations within two hours. It is metabolised by hepatic hydroxylation and oxidation. Its metabolites (unlike troglitazone) are not hepatotoxic and have dual biliary and renal elimination (55% and 45% respectively). No dose adjustment is necessary with renal impairment.[9,10]

9.2.5 Glycaemic efficacy[11,12]

As monotherapy (vs. placebo): reduces HbA_{1c} by a mean of -0.9% (up to -1.7%)[11,12] and is as effective as metformin.[13]

As dual therapy: reduces HbA_{1c} by a mean of -1.2% (up to -1.7%)[11,12] and not different to gliclazide over 2 years.[14]

As triple therapy: reduces HbA_{1c} by a mean of 0.9% (up to -1.5%)

The durability of glycaemic control over three years has been shown to be better with rosiglitazone than glibenclamide[15] and better for pioglitazone versus gliclazide over 2 years.[14]

9.2.6 Hypoglycaemia

Pioglitazone being an insulin sensitiser enhances the action of endogenous insulin which remains glucose-dependent (in the absence of therapy with insulin and insulin secretagogues). It does not cause significant hypoglycaemia when used as monotherapy or when combined with other non-hypoglycaemia provoking drugs (e.g. metformin, DPP-4 inhibitors, SGLT2 inhibitors, alpha-glucosidase inhibitors).[12]

9.2.7 Weight

Data from a meta-analysis the average weight gain with pioglitazone as monotherapy was 2-3 kg over 1 year and 1.5 kg when added to metformin.[10] The mean weight gain with

pioglitazone over the three years of the PROactive study was 3.6 kg.[16] Weight gain with pioglitazone is dose dependent.[17]

Pioglitazone's action on PPARγ receptors in adipose tissue leads to adipocyte differentiation and improved insulin sensitivity, both of which contribute to weight gain. The mechanism includes fluid retention and an increase in adipose tissue mass but the relative contribution of each mechanism is debated. Imaging studies consistently report a greater increase in peripheral adiposity and some studies have even reported a reduction in visceral adiposity.[9] The increase in adiposity may be integral to the action of TZDs rather than an unwanted side effect. Improvements in insulin sensitivity, glycaemic control and cardiovascular outcomes have been positively correlated with weight gain.[18,19]

9.2.8 Microvascular and macrovascular outcomes

The PROactive study was a secondary prevention prospective, RCT that assigned 5238 patients with type 2 diabetes and existing macrovascular disease equally to pioglitazone or placebo, in addition to their glucose-lowering drugs and other medications. The primary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and lower limb amputation. Average duration of follow-up was 34.5 months. The composite primary endpoint was reduced by10% and was not significant due to the number of peripheral vascular interventions (considered a "soft endpoint"). The main secondary endpoint, the composite of all-cause mortality, non-fatal myocardial infarction, and stroke was reduced by 16% and was statistically significant. Essentially pioglitazone reduced all cardiovascular endpoints except peripheral vascular revascularisations.[16]

The results from pre-specified post-hoc analyses of subgroups in PROactive reported the following results: the 2,445 patients with previous myocardial infarction had a significant 28% decrease in recurrent MI and the 984 patients with previous strokes had a significant 47% reduction in recurrent stroke.[20,21] Patients with CKD (eGFR <60 ml/min) also had better outcomes for both the primary and secondary endpoints, and similar benefit was also demonstrated in a retrospective study of dialysis-requiring patients.[22,23] Only the patients with PAD at baseline in PROactive did not benefit from pioglitazone.[24]

A 2007 meta-analysis of RCTs of pioglitazone reported an 18% relative risk reduction in the composite outcome (death, myocardial infarction, or stroke).[25] In a 2017 meta-analysis including 9 trials with 12 026 participants pioglitazone therapy was associated with a significantly lower risk of major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke and cardiovascular death), both in patients with pre-diabetes or insulin resistance, as well as those with type 2 diabetes by 23% and 17% respectively.[26]

Observational studies have also reported significantly improved cardiovascular outcomes for pioglitazone compared to rosiglitazone, as well as metformin and SUs.[27–29]

Pioglitazone is consistently associated with increased rates of hospitalisation for heart failure in CV outcomes trials when compared to placebo, but mortality for heart failure is not increased.[16,25,30] In PROactive this meant that 5.7% of pioglitazone treated patients vs. 4.1% of patients receiving placebo developed heart failure (absolute risk increase = 1.6%). Patients older than 65 years taking concomitant pioglitazone and insulin had the highest rate of CHF (9.7% for pioglitazone + insulin, 8.2% for insulin, 4.0% for placebo).[10,16] The mechanism for CHF is with TZDs is the fluid retention that occurs in susceptible patients; there is no evidence of cardiac toxicity.[30] This mechanism may also accounts for the slightly higher rates of macular oedema noted in some trials.[31]

In summary, pioglitazone has been consistently associated with improved macrovascular outcomes but is also associated with higher rates of fluid retention, oedema and heart failure.

9.2.9 Pleiotropic effects and non-glycaemic benefits

Lipids: Pioglitazone treatment is consistently associated with improvements in triglycerides (-5 to -10%), HDL-cholesterol (+10 to +20%) and free fatty acids. Its effect on total and LDL-cholesterol is neutral but it does change small dense LDL particles to larger more buoyant (less atherogenic) particles. It also tends to lower atherogenic apo-B100 containing particles.[32,33] These effects are different to those seen with rosiglitazone which is associated with a more atherogenic lipid profile. These are the main reasons postulated for the better CV outcomes noted with pioglitazone versus rosiglitazone.

Blood pressure: Pioglitazone produces small but consistent reductions in systolic and diastolic blood pressure (3–5 mmHg after 12 months when added to either glimepiride or metformin).[34]

Non-traditional risk factors for CVD: Pioglitazone lowers C-reactive protein, increases plasminogen activator inhibitor-1 [PAI-1], increases adiponectin (anti-atherogenic), modulates plaque stability and improves endothelial function. Pioglitazone was also associated with significant reductions in microalbuminuria in the QUARTET studies when compared to metformin or gliclazide over 1-2 years.[13,14] The clinical significance of these findings is supported by evidence of improved endothelial function, reduced carotid intima media thickness, and improvements in atheroma volume after coronary artery stent implantation (the CHICAGO and PERISCOPE trials using glimepiride as comparator).[30]

Non-alcoholic steatohepatitis (NASH): It is estimated that 20-80% of obese type 2 diabetes patients have non-alcoholic fatty liver disease and that about 30% of these individuals have the more severe and progressive form (NASH). NAFLD is the leading cause of chronic liver disease worldwide, and is currently the 3rd leading indication for liver transplantation.[35,36] Pioglitazone is the only drug proven to improve and reduce fibrosis in NASH and is currently the drug of choice in diabetes patients with NASH.[37] Paradoxically pioglitazone therapy itself can occasionally be associated with elevations of liver enzyme levels to above three times the upper normal limit. Abnormal liver function, if present, should be investigated prior to initiating treatment for diabetes

with pioglitazone. If the abnormality is due to NAFLD/NASH this would not constitute a contraindication to pioglitazone treatment; on the contrary it may be a compelling indication for its use. Patients suspected of having NASH should however be referred to a specialist as liver biopsy may be necessary prior to initiating therapy.

Pioglitazone treatment should be stopped if liver enzyme elevations to more than three times the upper normal limit occur after initiating therapy.

Polycystic ovary syndrome (PCOS): Pioglitazone improves the insulin resistance associated with PCOS and may restore ovulation in anovulatory patients, and improve the concomitant metabolic abnormalities.[38,39] These patients should be warned of this possibility.

9.1.7 Adverse Effects and Special Precautions

The clinical use of pioglitazone is limited by the risk of adverse events, including weight gain, CHF, bone fractures, and possibly bladder cancer.

Fluid retention, peripheral oedema and congestive heart failure

PPAR gamma receptors are present in the distal renal cortical collecting tubules and the TZDs lead to salt and water retention which may lead to fluid retention.[30] This can lead to haemodilution (reduced haematocrit), peripheral oedema (~ 5% of users), and in susceptible patients (e.g. those with diastolic dysfunction or undiagnosed CHF) may precipitate or exacerbate overt heart failure. This incidence of fluid retention, peripheral oedema and cardiac failure is higher when pioglitazone is combined with insulin, and is also dose dependent. Peripheral oedema is rarely responsible for discontinuing pioglitazone (<1%) and responds to diuretic therapy.

Pioglitazone should not be prescribed to patients at risk for CHF (history of any heart failure, diastolic dysfunction, elevated levels of pro-BNP, unexplained oedema or age >75 years).

Bone fractures

TZDs have been associated with a higher risk of long bone fractures. A pooled analysis of adverse reactions from double-blind RCTs in over 8100 pioglitazone and 7400 comparator treated patients reported an increased incidence in bone fractures in women on pioglitazone for up to 3.5 years. Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator.

The calculated fracture incidence from this pooled dataset was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The excess risk of fractures for women on pioglitazone is therefore 0.8 fractures for every 100 patients treated for one year. In the PROactive study over 3.5 years the excess fracture risk was 0.5 fractures per 100 patient-years.

Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women.[10]

The fractures are not at typical osteoporotic sites of spine and hip but instead distal fractures of the upper and lower extremities.[9] The mechanism for fractures may involve PPARγ effects on mesenchymal cell differentiation in bone and there does appear to be a cumulative dose effect on bone density with time. The effects of TZDs on bone and fracture have been reviewed in detail.[40]

At present the risk appears small but definite, and pioglitazone should be avoided in patients with osteoporosis. Pioglitazone should also not be prescribed to women or men with risk factors for osteoporosis or fracture unless their bone density can be monitored.

Bladder Cancer

Adverse event reporting to the FDA initially suggested a small but non-significant risk of bladder cancer with pioglitazone from Kaiser Permanente in 2011.[41] In 2012 a French registry reported an increase in bladder cancer risk with pioglitazone and SEMDSA opted not to include pioglitazone as therapeutic option for primary care.[42]

A six year follow-up of the PROactive study reported no excess cases of bladder cancer after excluding patients in whom exposure to study drug was less than one year.[43] Similarly a 16 year follow-up of the initial report from Kaiser Permanente in 2015 did not confirm the initial report increased bladder cancer risk.[44] These follow-up studies in patients who have continued to receive pioglitazone argue against a cumulative dose effect. Overall, the weight of current evidence cannot exclude a small increase in bladder cancer risk. At worst, from the French cohort study the risk of bladder cancer with pioglitazone treatment would increase from 42.8 to 49.4 cases of bladder cancer per 100,000 person years i.e. 6.6 extra cases for every 100 000 patients treated with pioglitazone for 1 year.

Risk factors for bladder cancer include heavy smoking, older age (>75 years), chronic cystitis, previous pelvic radiation and cyclophosphamide use. To mitigate against any risk of bladder cancer, pioglitazone should not be prescribed to these high-risk patients and those with unexplained haematuria.

9.2.10 Recommendations

Indications

1. Consider pioglitazone as initial monotherapy in patients who have intolerable side-effects with metformin and its extended-release formulation, or when metformin is contraindicated.
2. Consider pioglitazone as add on (second-line) to metformin (or other initial drug therapy) in patients not achieving or maintaining their glycaemic targets, especially if:
    a. The patient is at high risk for hypoglycaemia and/or its consequences.
    b. There has been a history of severe hypoglycaemia or recurrent mild hypoglycaemia with gliclazide MR use.
    c. The patient has a history of a previous myocardial infarct, previous stroke or chronic kidney disease stage 3.

3. Consider pioglitazone as a third glucose lowering drug in patients not achieving or maintaining their glycaemic targets on a two drug regimen that does not already include pioglitazone. Inform the patient that in South Africa this constitutes an "off-label" prescription but that the drug is registered for this indication outside of South Africa, and its use in this situation is endorsed by international guidelines.[45,46]
4. The presence of NASH may be a compelling indication to use pioglitazone at any stage of diabetes; NASH should be managed in conjunction with a specialist (endocrinologist or hepatologist).

Dosing

Pioglitazone is available in 15 mg and 30 mg tablets. Start with 15 mg or 30 mg administered once daily usually with the morning meal. The dose can be titrated every 1-3 months based on fasting glucose and HbA_{1c} targets, as well as side effects. Fluid retention and (and the weight gain due it) are dose dependent side effects. Maximum dose is 45 mg if tolerated.

Prescribing in chronic kidney disease

No dose adjustments are necessary for CKD and pioglitazone has demonstrated significantly improved CV outcomes in patients with CKD and those on dialysis.[22,23] However the risk of fluid retention is greater and for this reason pioglitazone should not be used at primary care level when the eGFR is less than 30 ml/min/1.73m^2.

Special precautions and side effects

Do not use pioglitazone at primary health care level if the patient:

1. Is > 75 years old (risk of CHF, fracture and bladder cancer)
2. Has a history of congestive heart failure, abnormal ejection fraction, diastolic dysfunction or unexplained oedema
3. Has a history of osteoporosis or has other risk factors for osteoporotic fractures (e.g. chronic corticosteroid or warfarin use; cigarette smoking, rheumatoid arthritis, cancer chemotherapy or radiotherapy, history of fragility fractures etc.). The menopause alone does not constitute a contra-indication although bone density measurements should be performed in these patients, as per osteoporosis guidelines, prior to initiating therapy.
4. Has a history of bladder cancer or haematuria that has not been investigated.
5. Has stage 4 or worse chronic kidney disease (risk of fluid retention).
6. Is using concomitant insulin therapy (risk of fluid retention).
7. Has elevated liver enzymes (ALT or AST > 2.5 times the upper normal limit) which have not been investigated.

Authors: Aslam Amod and Fraser Pirie
Editors: Zaheer Bayat, Ankia Coetzee, Nazeer A Mohamed, Joel A Dave, Tanya E Kinvig

References

1. Gale EAM. Troglitazone: the lesson that nobody learned? Diabetologia. 2006;49(1):1-6. doi:10.1007/s00125-005-0074-6.
2. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Engl J Med. 2007;356(24):2457-2471. doi:10.1056/NEJMoa072761.
3. South African Government. Withdrawal of rosiglitazone-containing medicines from South African market. July 2011. http://www.gov.za/withdrawal-rosiglitazone-containing-medicines-south-african-market. Accessed June 22, 2016.
4. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373(9681):2125-2135. doi:10.1016/S0140-6736(09)60953-3.
5. FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines. December 2015. https://www.fda.gov/drugs/drugsafety/ucm376389.htm. Accessed June 22, 2016.
6. Bach RG, Brooks MM, Lombardero M, et al. Rosiglitazone and Outcomes for Patients With Diabetes Mellitus and Coronary Artery Disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. Circulation. 2013;128(8):785-794. doi:10.1161/CIRCULATIONAHA.112.000678.
7. Amod A, Ascott-Evans BH, Berg GI, et al. The 2012 SEMDSA Guideline for the Management of Type 2 Diabetes (Revised). J Endocrinol Metab Diabetes South Africa. 2012;17(2):S1-S95.
8. Gillies PS, Dunn CJ. Pioglitazone. Drugs. 2000;60(2):333-343. doi:10.2165/00003495-200060020-00009.
9. Soccio RE, Chen ER, Lazar MA. Thiazolidinediones and the Promise of Insulin Sensitization in Type 2 Diabetes. Cell Metab. 2014;20(4):573-591. doi:10.1016/j.cmet.2014.08.005.
10. European Medicines Agency. Actos: EPAR Product Information. June 2016. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000285/WC500021386.pdf. Accessed October 25, 2016.
11. Filipova EP, Uzunova KH, Vekov TY. Comparative analysis of therapeutic efficiency and costs (experience in Bulgaria) of oral antidiabetic therapies based on glitazones and gliptins. Diabetol Metab Syndr. 2015;7(1):63. doi:10.1186/s13098-015-0059-7.
12. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes. JAMA. 2016;316(3):313. doi:10.1001/jama.2016.9400.
13. Schernthaner G, Matthews DR, Charbonnel B, Hanefeld M, Brunetti P. Efficacy and Safety of Pioglitazone Versus Metformin in Patients with Type 2 Diabetes Mellitus: A Double-Blind, Randomized Trial. J Clin Endocrinol Metab. 2004;89(12):6068-6076. doi:10.1210/jc.2003-030861.
14. Charbonnel B, Schernthaner G, Brunetti P, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. Diabetologia. 2005;48(6):1093-1104. doi:10.1007/s00125-005-1751-1.
15. Kahn SE, Haffner SM, Heise M a, et al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. N Engl J Med. 2006;355(23):2427-2443. doi:10.1056/NEJMoa066224.
16. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279-1289. doi:10.1016/S0140-6736(05)67528-9.
17. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione Use, Fluid Retention, and Congestive Heart Failure: A consensus statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2004;27(1):256-263. doi:10.2337/diacare.27.1.256.
18. Miyazaki Y, De Filippis E, Bajaj M, et al. Predictors of improved glycaemic control with rosiglitazone therapy in type 2 diabetic patients: a practical approach for the primary care physician. Br J Diabetes Vasc Dis. 2005;5(1):28-35. doi:10.1177/14746514050050010601.
19. Doehner W, Erdmann E, Cairns R, et al. Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: An analysis of the PROactive study population. Int J Cardiol. 2012;162(1):20-26. doi:10.1016/j.ijcard.2011.09.039.
20. Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM. The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2,445 Patients With Type 2 Diabetes and Previous Myocardial Infarction. J Am Coll Cardiol. 2007;49(17):1772-1780. doi:10.1016/j.jacc.2006.12.048.

21. Wilcox R, Bousser M-G, Betteridge DJ, et al. Effects of Pioglitazone in Patients With Type 2 Diabetes With or Without Previous Stroke: Results From PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke. 2007;38(3):865-873. doi:10.1161/01.STR.0000257974.06317.49.
22. Schneider CA, Ferrannini E, DeFronzo R, Schernthaner G, Yates J, Erdmann E. Effect of Pioglitazone on Cardiovascular Outcome in Diabetes and Chronic Kidney Disease. J Am Soc Nephrol. 2008;19(1):182-187. doi:10.1681/ASN.2007060678.
23. Brunelli SM, Thadhani R, Ikizler TA, Feldman HI. Thiazolidinedione use is associated with better survival in hemodialysis patients with non-insulin dependent diabetes. Kidney Int. 2009;75(9):961-968. doi:10.1038/ki.2009.4.
24. Dormandy JA, Betteridge DJ, Schernthaner G, Pirags V, Norgren L, PROactive investigators. Impact of peripheral arterial disease in patients with diabetes—Results from PROactive (PROactive 11). Atherosclerosis. 2009;202(1):272-281. doi:10.1016/j.atherosclerosis.2008.03.002.
25. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus. JAMA. 2007;298(10):1180. doi:10.1001/jama.298.10.1180.
26. Liao H-W, Saver JL, Wu Y-L, Chen T-H, Lee M, Ovbiagele B. Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: a systematic review and meta-analysis. BMJ Open. 2017;7(1):e013927. doi:10.1136/bmjopen-2016-013927.
27. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, et al. Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone. JAMA. 2010;304(4):411. doi:10.1001/jama.2010.920.
28. Tannen R, Xie D, Wang X, Yu M, Weiner MG. A new 'Comparative Effectiveness' assessment strategy using the THIN database: comparison of the cardiac complications of pioglitazone and rosiglitazone. Pharmacoepidemiol Drug Saf. 2013;22(1):86-97. doi:10.1002/pds.3360.
29. Tzoulaki I, Molokhia M, Curcin V, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ. 2009;339(dec03 1):b4731-b4731. doi:10.1136/bmj.b4731.
30. John Betteridge D. CHICAGO, PERISCOPE and PROactive: CV risk modification in diabetes with pioglitazone. Fundam Clin Pharmacol. 2009;23(6):675-679. doi:10.1111/j.1472-8206.2009.00741.x.
31. Idris I, Warren G, Donnelly R. Association Between Thiazolidinedione Treatment and Risk of Macular Edema Among Patients With Type 2 Diabetes. Arch Intern Med. 2012;172(13):1005-1011. doi:10.1001/archinternmed.2012.1938.
32. Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005;28(7):1547-1554.
33. Deeg MA, Buse JB, Goldberg RB, et al. Pioglitazone and Rosiglitazone Have Different Effects on Serum Lipoprotein Particle Concentrations and Sizes in Patients With Type 2 Diabetes and Dyslipidemia. Diabetes Care. 2007;30(10):2458-2464. doi:10.2337/dc06-1903.
34. DEROSA G, FOGARI E, CICERO AFG, et al. Blood Pressure Control and Inflammatory Markers in Type 2 Diabetic Patients Treated with Pioglitazone or Rosiglitazone and Metformin. Hypertens Res. 2007;30(5):387-394. doi:10.1291/hypres.30.387.
35. Rinella ME. Nonalcoholic Fatty Liver Disease. JAMA. 2015;313(22):2263. doi:10.1001/jama.2015.5370.
36. EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388-1402. doi:10.1016/j.jhep.2015.11.004.
37. Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis. JAMA Intern Med. 2017;61(4):1392-1405. doi:10.1001/jamainternmed.2016.9607.
38. OTA H, GOTO T, YOSHIOKA T, OHYAMA N. Successful pregnancies treated with pioglitazone in infertile patients with polycystic ovary syndrome. Fertil Steril. 2008;90(3):709-713. doi:10.1016/j.fertnstert.2007.01.117.
39. Sangeeta S. Metformin and Pioglitazone in Polycystic Ovarian Syndrome: A Comparative Study. J Obstet Gynecol India. 2012;62(5):551-556. doi:10.1007/s13224-012-0183-3.
40. Yau H, Rivera K, Lomonaco R, Cusi K. The Future of Thiazolidinedione Therapy in the Management of Type 2 Diabetes Mellitus. Curr Diab Rep. 2013;13(3):329-341. doi:10.1007/s11892-013-0378-8.
41. Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the Association of Pioglitazone Use and Bladder Cancer Through Drug Adverse Event Reporting. Diabetes Care. 2011;34(6):1369-1371. doi:10.2337/dc10-2412.
42. Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. Diabetologia. 2012;55(7):1953-1962. doi:10.1007/s00125-012-2538-9.
43. Erdmann E, Song E, Spanheimer R, van Troostenburg de Bruyn A-R, Perez A. Observational follow-up of the PROactive study: a 6-year update. Diabetes, Obes Metab. 2014;16(1):63-74. doi:10.1111/dom.12180.
44. Lewis JD, Habel LA, Quesenberry CP, et al. Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons With Diabetes. JAMA. 2015;314(3):265. doi:10.1001/jama.2015.7996.
45. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycaemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a position statement of the american diabetes association and the european association for the study of diabetes. Diabetes Care. 2015;38(1):140-149. doi:10.2337/dc14-2441.
46. American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment. Sec. 8. In Standards of Medical Care in Diabetes 2017. Diabetes Care. 2017;40(Supplement 1):S64-S74. doi:10.2337/dc17-S011.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 9.4: Drug review - Dipeptidyl peptidase-4 inhibitors

SEMDSA Type 2 Diabetes Guideline Expert Committee

Introduction to incretin-based therapies

Incretins are hormones that are secreted into the circulation within minutes of exposure of the gastrointestinal tract lumen to ingested nutrients, resulting in augmentation of insulin release from the pancreatic beta-cells in a glucose-dependent manner. Two incretins have been identified as having an important role to play in glucose homeostasis. These are glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP). Both GLP-1 and GIP are responsible for the observed "incretin effect" which is characterised by oral glucose having a greater stimulatory effect on of insulin secretion than intravenous glucose. The net effect of incretin production is to increase insulin-mediated glucose disposal in peripheral tissues and to suppress hepatic glucose production, both of which result in lowering of blood glucose. GLP-1 also suppresses glucagon production and, in pharmacological doses, can delay gastric emptying and reduce food intake. GLP-1 levels are abnormally low in patients with type 2 diabetes mellitus. Two classes of pharmaceutical agents exploit the beneficial effects of GLP-1 and include the dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists. The DPP-4 inhibitors constitute a relatively new class of agents that enhance the options available for anti-hyperglycaemic therapy and are capable of addressing some of the unmet needs in diabetes.

9.4.1 Mode of action of DPP-4 inhibitors

Endogenous GLP-1 has a short half-life of one to two minutes, as a result of rapid in-vivo degradation by the enzyme DPP-4. DPP-4 inhibitors are capable of inhibiting the degradation of endogenous GLP-1, thereby therapeutically raising circulating GLP-1 levels. When used alone, DPP-4 inhibitors do not cause hypoglycaemia, because its effects on insulin and glucagon secretion are glucose dependent.

9.4.2 Pharmacology

Table I compares the pharmacological properties of the three DPP-4 inhibitors that are available in South Africa. All of the DPP-4 inhibitors are dosed once daily with the exception that vildagliptin is dosed twice daily when not combined with a sulphonylurea.

9.4.3 Glycaemic efficacy

There are three DPP-4 inhibitors currently registered in South Africa and these drugs are all administered orally, once or twice daily. They have differing pharmacokinetic profiles but

Table I: Comparison of available DPP-4 inhibitors

DPP-4 inhibitor	Saxagliptin	Sitagliptin#	Vildagliptin*
Trade name	Onglyza®	Januvia®	Galvus®
Half-life (t ½)	±2.5 hrs	±12 hrs	1.5-3 hrs
Usual Dose	5 mg once daily	100 mg once daily	50 mg once/twice daily*
Tablet size	2.5 mg, 5 mg	25 mg, 50 mg, 100 mg	50 mg
HbA1c Reduction$ (%) [95% CI] Monotherapy Add-on to Met Add-on to SU Add-on to SU+Met	 ~ 0.59 [–0.8 to –0.38] ~ 0.58 [–0.76 to –0.41] ~ 0.72 [–1.22 to –0.22] -	 ~ 0.78 [–0.95 to –0.62] ~ 0.65 [–0.78 to –0.52] ~ 0.67 [–0.90 to –0.45] ~ 0.89 [–2.41 to 0.63]	 ~ 0.6 [–0.80 to –0.40] ~ 0.48 [–0.92 to –0.05] ~ 0.83 [–1.07 to –0.61] ~ 0.76 [–1.01 to –0.51]
Liver Metabolism	Liver metabolism Contraindicated in severe hepatic impairment	Minimal. No dose adjustment with hepatic impairment but caution advised.#	Contraindicated in moderate to severe liver impairment
Renal dose	GFR< 50 ml/min 2.5 mg once daily	GFR <50 ml/min 50 mg once daily GFR <30 ml/min 25 mg once daily	GFR <50 ml/min 50 mg once daily
Adverse effects	Headache, nasopharyngitis, urinary tract infections	diarrhoea, nausea, nasopharyngitis	Dizziness, nasopharyngitis
SEP at maximum dose	R 256.22	R 322.10	R 347.87

*Dose is 50 mg once daily when combined with a sulphonylurea; twice daily dosing is needed without sulphonylurea use.
Despite the lack of hepatic metabolism, use with caution in moderate hepatic impairment and not recommended in severe hepatic impairment
$ Weighted mean difference at usual dose[1]
SEP - single exit price[2]
Table adapted from Chen et al[3]

appear to have similar efficacy, and will reduce HbA_{1C} modestly, by approximately 0.5-1.1% compared to placebo. Their main advantages are weight neutrality and the relatively low propensity for hypoglycaemia.

9.4.4 Microvascular outcomes

There have been no microvascular outcome studies with DPP-4 inhibitor therapy.

9.4.6 Macrovascular and mortality outcomes

Three studies (SAVOR-TIMI 53, EXAMINE and TECOS) using DPP-4 inhibitors were designed to assess cardiovascular outcomes using these newer agents.[4–6] All three studies revealed no increased cardiovascular risk and mortality rates were not elevated. However, an increased rate of hospitalisation for cardiac failure was significant in the SAVOR -TIMI 53 trial with saxagliptin, but this finding remains unexplained and merits further evaluation.[5] Results from the CAROLINA and CARMELINA trials using linagliptin, are expected in 2018 and may provide more insight into the long-term outcomes associated with these agents. In the meantime, saxagliptin should not be prescribed in patients with, or at high risk for heart failure (e.g. severe coronary disease, known to have elevated pro-BNP).

9.4.5 Adverse events and precautions

The DPP-4 inhibitors are usually well tolerated.

Infrequent: Infrequently reported side-effects in clinical trials include upper respiratory infection, nasopharyngitis and headache.

Rare: Rare cases of pancreatitis have been reported in adverse event databases raising concerns about safety but observational studies have been inconclusive. Furthermore, recently published results from three large randomised controlled trials using saxagliptin, alogliptin and sitagliptin (SAVOR-TIMI 53, EXAMINE and TECOS respectively), have individually not shown an increased risk of pancreatitis.[4–6] A meta-analysis of the trials suggests a statistically significant risk of pancreatitis, however the absolute risk is small. DPP-4 inhibitors are contraindicated a history of a serious hypersensitivity reaction to DPP-4 inhibitors, a history of acute, chronic or recurring pancreatitis, and those with pancreatic cancer.

9.4.7 Recommendations for DPP-4-inhibitor use

DPP-4 inhibitors can be employed as monotherapy in patients intolerant of metformin or where metformin use is undesirable. DPP-4 inhibitors can be used in combination with metformin as second-line agents, with a low risk of hypoglycaemia and weight neutrality being advantageous. Some DPP-4 inhibitors are approved for addition as third-line therapy after metformin and sulphonylurea or pioglitazone. They may be preferred in situations when the risk of hypoglycaemia or its consequences are too high, or when tolerability/adverse event risk limits the use of other treatment options. Some DPP-4 inhibitors are also available in fixed-dose combination tablets with standard-release metformin; these are dosed twice daily. The lower pill burden of a fixed-dose combination without the risk of hypoglycaemia, may improve adherence and facilitate targeting a lower HbA_{1C} safely.

Author: Imran Paruk
Editor: Aslam Amod

References

1. Craddy P, Palin H-J, Johnson KI. Comparative Effectiveness of Dipeptidylpeptidase-4 Inhibitors in Type 2 Diabetes: A Systematic Review and Mixed Treatment Comparison. Diabetes Ther. 2014;5(1):1-41. doi:10.1007/s13300-014-0061-3.
2. South African Medicine Price Registery. Database Of Medicine Prices 14th March 2017. http://www.mpr.gov.za/Publish/ViewDocument.aspx?DocumentPublicationId=3285. Accessed March 20, 2017.
3. Chen X-W, He Z-X, Zhou Z-W, et al. Clinical pharmacology of dipeptidyl peptidase 4 inhibitors indicated for the treatment of type 2 diabetes mellitus. Clin Exp Pharmacol Physiol. 2015;42(10):999-1024. doi:10.1111/1440-1681.12455.
4. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015;373(3):232-242. doi:10.1056/NEJMoa1501352.
5. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. N Engl J Med. 2013;369(14):1317-1326. doi:10.1056/NEJMoa1307684.
6. Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327-1335. doi:10.1056/NEJMoa1305889.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Appendix 9.5: Drug review - GLP-1 receptor agonists

SEMDSA Type 2 Diabetes Guideline Expert Committee

The incretin effect is discussed in the introduction to incretin based therapies above (Appendix 9.4). The main advantage of GLP-1 receptor agonists (GLP-1RA) is glycaemic efficacy without weight gain or hypoglycaemia. Their non-glycaemic benefits include positive effects on weight loss, blood pressure and cholesterol levels.

9.5.1 Mode of action

GLP-1RAs are modified GLP-1 molecules are modified GLP-1 molecules that have structural homology with endogenous GLP-1 but are resistant to the enzymatic cleavage by DPP-4, resulting in a longer duration of action. Pharmacological dosing and prolongation of the half-life results in persistent supra-physiological levels of GLP-1, which increases insulin secretion, decreases glucagon release, enhances satiety and delays gastric emptying.

9.5.2 Pharmacology

Table I compares the pharmacological and other properties of the two available in South Africa. They are both available only as injectables in the form of multi-dose pens, and are administered by subcutaneous injection; liraglutide is dosed once daily while exenatide is administered twice daily. The peak exenatide concentrations after meals results in a better post-prandial glucose lowering compared to liraglutide which has better efficacy at lowering fasting glucose.[1] This difference can be useful therapeutically in selected patients.

9.5.3 Glycaemic efficacy and clinical use

Exenatide and liraglutide are examples of GLP-1RAs that are currently available in South Africa. The main advantage is that unlike most other diabetes drugs, the GLP-1RAs promote weight loss and do not cause hypoglycaemia when used alone. The GLP-1RAs are approved for combination therapy with metformin

Table I: Comparison of available GLP-1 receptor agonists

GLP-1 receptor agonist	Exenatide	Liraglutide
Trade name	Byetta®	Victoza®
Amino acid sequence similarity to native GLP-1	53%	97%
Half-life (t ½)	2.5 hrs	11-15 hrs
Starting dose	5 ug BD for 4 weeks	0.6 mg OD for 1 week
Usual Dose	10 ug BD	1.2 mg OD Max dose 1.8 mg OD
Route	subcutaneous	subcutaneous
Timing of dose	Within 60 min before morning & evening meal; not after a meal	Any time of the day
HbA1c reduction (%)	~ 0.8 %[2,3]	1.2 mg – 0.8%[1,4] 1.8 mg – 1.1-1.3%[1]
Weight reduction (kg)	1.1-2.9 kg	2.1-2.6 kg
Non-responders (no weight loss)[1]	~ 25%	~25%
Renal dose	Do not use if eGFR <30ml/min	No dose adjustment required **
Adverse effects[1] - Diarrhoea (%) - Nausea (%) - Vomiting (%)	 12.1 28.0 9.9	 12.3 25.5 6.0
Single exit price (SEP)	R 617.75 (10ug BD)	R 1430.61 (1.2 mg OD) R 2145.97 (1.8 mg OD)

When using a GLP-1RA in combination with sulphonylureas, a lower dose of sulphonylurea may be required as hypoglycaemia may occur more frequently.
**Post-marketing reports of acute kidney injury reported in patients with pre-existing kidney disease. Use with caution in patients with chronic kidney disease.

and/or sulphonylureas. However, adding a GLP-1RA also remains an attractive option to intensify insulin therapy, especially when basal insulin is failing. Advantages of adding a GLP-1RA may include a reduction in total insulin requirements, lower risk of hypoglycaemia and possible weight-loss/prevention of weight gain when compared to intensifying insulin therapy with premix, basal-plus or basal-bolus. A systematic review and meta-analysis of randomised control trials comparing the combination of GLP-1RA and basal inulin to intensifying insulin therapy alone found greater reductions in HbA_{1C} with combination therapy (WMD -0.47%; 95% CI -0.59 to -0.35) and a significant weight-loss advantage (WMD -2.5 kg; 95% CI -3.3 to -1.7).[5] Exenatide is registered for add-on therapy to basal insulin with or without oral antidiabetic therapy in South Africa. Exenatide is initiated at a dose of 5 ug BD, any time within 60 minutes before the morning and evening meals, but the maximum and most effective dose is 10ug BD. The most cost-effective dose of liraglutide is 1.2 mg, as the 1.8 mg is only marginally more effective in lowering HbA_{1C}.[6–8]

The LEAD 6 study compared Liraglutide 1.8 mg and exenatide 10 ug twice daily as add-on therapy to metformin + sulphonylurea.[1] The mean HbA_{1C} reduction was -1.1% for liraglutide vs. -0.8% for exenatide. Mean weight loss was similar (~3kg). Discontinuation rates for liraglutide and exenatide were 14% and 19%, and more subjects experienced severe and serious adverse events with liraglutide (29/235) than exenatide (17/232); nausea was less persistent with liraglutide.[1] There are no clinical trials comparing liraglutide 1.2 mg OD with exenatide 10 ug BD.

9.5.4 Microvascular outcomes

There are no dedicated microvascular outcome studies for GLP-1RAs. In the LEADER trial the incidence of a composite exploratory outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (hazard ratio, 0.84; 95% CI, 0.73 to 0.97; P=0.02).[9] This benefit was driven by lower rates of renal outcomes, such as new-onset persistent macroalbuminuria. With moderate differences in glycaemic control between the trial groups over a median 3.8 years of follow-up, the achievement of renal microvascular benefits raises uncertainty about whether this is related to better glycaemic control or a drug effect. In the LEADER trial, there was also a higher rate of retinopathy events with liraglutide than with placebo (HR 1.15), although the difference was not significant.[9] However, in the SUSTAIN 6 trial (using the GLP-1RA semaglutide), there was an unexpected higher rate of retinopathy complications in the semaglutide group though the actual overall numbers were small.[10] There remains uncertainty about the microvascular effects of GLP-1RAs and more long-term studies addressing this issue are needed.

9.5.5 Macrovascular and mortality outcomes

The cardiovascular outcomes trials with GLP-1RAs are all safety trials which have been mandated by regulatory authorities, and were primarily designed to demonstrate cardiovascular safety of the product when compared to conventional treatments plus placebo, at equivalent HbA_{1C}, i.e. the trials are meant to test the safety of the drug, not the effect of improved glycaemic control. All of these trials recruited patients with either established cardiovascular disease or those who had multiple risk factors for cardiovascular disease. Results of these outcome trials are summarised in Table II. In the ELIXA trial, lixisenatide was non-inferior to conventional glucose lowering therapy.[11] In the LEADER trial, liraglutide 1.8 mg was superior to conventional treatment, and was associated with a 13% relative risk reduction (RRR) in the primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke – 3 point MACE) compared to placebo.[9] HbA_{1C} was not equivalent as there was a significant 0.4% HbA_{1C} difference in in favour of liraglutide, so it is not possible to conclude whether the improvement was the result of better glycaemic control or a specific effect of the drug. The beneficial effect on the composite outcome was driven by a reduction in cardiovascular mortality (RRR=22%) and all cause mortality (RRR=15%); there was no difference in rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalisation for heart failure. The calculated numbers needed to treat (NNT) to prevent one MACE, CV death and all cause death with liraglutide 1.8 mg were 66, 104 and 98 respectively.

In the SUSTAIN-6 trial the treatment effect of semaglutide 0.5 and 1.0 mg (not yet available in South Africa) for a relatively short duration (2.1 years) in diabetic patients with high CV risk, resulted in a significant 26% lower risk of the primary composite outcome than did those receiving placebo.[10] Similar to the LEADER trial, there was a significant HbA_{1C} difference between treatment groups. In both SUSTAIN-6 and LEADER, the subgroups of patients without established cardiovascular disease did not benefit significantly from the intervention. There are no cardiovascular outcomes trials with exenatide. The EXSCEL trial is currently underway to examine the long-term effects of exenatide-LAR 2 mg weekly on cardiovascular and mortality outcomes.

GLP-1RAs are consistently associated with slight blood pressure lowering.The conclusion is that liraglutide and semaglutide have proven cardiovascular safety, and has evidence for improved cardiovascular outcomes when used to improve glycaemic control in patients with established cardiovascular disease.

9.5.6 Adverse events and precautions

Common: The common side-effect on initiating GLP-1RA therapy is nausea and vomiting in up to 25% patients and this can be severe in some cases, leading to discontinuation in some (5-10%). It is usually transient (four to eight weeks), can be minimised by titrating up the dose slowly, and it responds to antiemetics. GLP-1RAs should probably be avoided in patients with significant gastrointestinal disease, particularly gastroparesis.

Rare but serious: Post-marketing reports of pancreatitis (<0.2%) with GLP-1RA therapy have emerged but it is not clear whether pancreatitis is directly related to therapy. A possible association with cholelithiasis may exist. Among the available GLP-1RA outcome studies which include SUSTAIN 6, LEADER and ELIXA studies, there were numerically higher numbers of patients with cancer of the pancreas in the GLP-1 treated groups compared to placebo, but this was not statistically significant.[9–11] Therefore until further information becomes available, these drugs are best avoided in patients with a past history of acute or chronic

Table III: Summary of GLP-1 agonist cardiovascular safety studies

Prospective cardiovascular outcome trials			
Study, drug used, no. of pts	**Study population**	**Primary end point; median follow-up period**	**Pooled point estimate [95% CI] §**
ELIXA[11] Lixisenatide 6068 pts	acute coronary event within the last 180 days	composite endpoint of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina; 25 months	1.02 [0.89–1.17]
LEADER[9] Liraglutide 9340 pts	High CV risk: (1) with prior CVD ≥50 years old and had one or more of the following CV comorbidities: concomitant CVD, cerebrovascular disease, PVD, chronic renal failure, or chronic heart failure; (2) without prior CVD ≥60 years old at screening and had one or more cardiovascular risk factors shown	primary composite endpoint of CV death, non-fatal MI or non-fatal stroke; 3.8 years	0.87 [CI 0.78–0.97]
SUSTAIN-6[10] Semaglutide 3297 pts	age ≥ 50 with estab. CVD (previous CV, cerebrovascular, or PVD), chronic heart failure (NYHA class II/III), or chronic kidney disease of stage 3 or higher or age ≥60 years with at least one CV risk factor	composite endpoint of CV death, nonfatal MI and non-fatal stroke; 2.1 years	0.74 [0.58–0.95]
Meta-analyses of cardiovascular safety			
Meta-analysis	**Type and no. of studies included**	**Outcome examined**	**Pooled point estimate [95%CI]§**
Ling Li et al[12], 2016	RCT - 20 studies	Incidence of heart failure	0.62 [0.31 to 1.22]

CI=confidence interval; RCT= randomized controlled trial; CV=cardiovascular; pts= patients, no= number; ITT= intention to treat
§95% Values <1.00 favour DPP-4 inhibitor safety; Confidence Interval: statistically significant if the interval does not cross 1.00

pancreatitis and pancreatic cancer, and in those at risk for pancreatitis (gallstones, pancreatic or biliary obstruction, or planned manipulation such as ERCP, excessive alcohol intake). Consider excluding cholelithiasis in high risk patients before adding GLP-1RA therapy. Patients should be warned to report symptoms suggestive of pancreatitis and discontinue the drug immediately on suspicion, and not to restart a GLP-1RA if the diagnosis of pancreatitis is confirmed. In animal models, liraglutide was associated with the development of C cell tumours. This has not yet been reported in humans. Nevertheless, liraglutide is contraindicated in patients with a history of MTC or multiple endocrine neoplasia (MEN) syndrome type 2.

9.5.7 Recommendations

GLP-1RAs are a useful addition to the currently available antihyperglycaemic therapies and have a novel mode of action with potential additional non-glycaemic benefits. They can be used as adjunctive therapy to the currently available oral agents to improve glycaemic control. Although they have been studied in combination with metformin as dual therapy, they do not offer substantial advantages over other less expensive therapeutic options in this circumstance, except in patients with established cardiovascular disease. Its routine use as a 2nd-line option for dual therapy is therefore not supported. However, they may be useful agents in selected patients as a 3rd glucose lowering drug (in combination with metformin + sulphonylurea or metformin + TZD). Furthermore, GLP-1RAs can also be used to advance insulin therapy when added to basal insulin; exenatide is registered for this indication, and may improve post-prandial and overall glucose control in patients who are not controlled on basal insulin. Adding a GLP-1RA to basal insulin may be preferred to intensifying insulin in some patients.[13–15]

Response to GLP-1RA therapy must be assessed at three and six months. Consider continuing GLP-1RA therapy only if there has been a reduction of at least 0.5% in HbA_{1C} and a weight loss of at least 3% of initial body weight at six months.

Because of their similar mode of action and lack of clinical trials, GLP-1RAs must not be combined with DPP-4 inhibitors. There are also no studies examining GLP-1RA combinations with SGLT2 inhibitors in type 2 diabetes.

Author: Imran Paruk
Editor: Aslam Amod

References

1. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009;374(9683):39-47. doi:10.1016/S0140-6736(09)60659-0.
2. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005;28(5):1092-1100.
3. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005;28(5):1083-1091.
4. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009;52(10):2046-2055. doi:10.1007/s00125-009-1472-y.
5. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and Glucagon-Like Peptide 1 Receptor Agonist Combination Therapy in Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Diabetes Care. 2017;40(4):614-624. doi:10.2337/dc16-1957.
6. Nauck M, Frid A, Hermansen K, et al. Efficacy and Safety Comparison of Liraglutide, Glimepiride, and Placebo, All in Combination With Metformin, in Type 2 Diabetes: The LEAD (Liraglutide Effect and Action in Diabetes)-2 study. Diabetes Care. 2009;32(1):84-90. doi:10.2337/dc08-1355.

7. Marre M, Shaw J, Brändle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009;26(3):268-278. doi:10.1111/j.1464-5491.2009.02666.x.
8. Zinman B, Gerich J, Buse JB, et al. Efficacy and Safety of the Human Glucagon-Like Peptide-1 Analog Liraglutide in Combination With Metformin and Thiazolidinedione in Patients With Type 2 Diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009;32(7):1224-1230. doi:10.2337/dc08-2124.
9. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827.
10. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141.
11. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med. 2015;373(23):2247-2257. doi:10.1056/NEJMoa1509225.
12. Li L, Li S, Liu J, et al. Glucagon-like peptide-1 receptor agonists and heart failure in type 2 diabetes: systematic review and meta-analysis of randomized and observational studies. BMC Cardiovasc Disord. 2016;16(1):91. doi:10.1186/s12872-016-0260-0.
13. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-Like Peptide 1 Receptor Agonist or Bolus Insulin With Optimized Basal Insulin in Type 2 Diabetes. Diabetes Care. 2014;37(10):2763-2773. doi:10.2337/dc14-0876.
14. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet. 2014;384(9961):2228-2234. doi:10.1016/S0140-6736(14)61335-0.
15. Buse JB, Bergenstal RM, Glass LC, et al. Use of Twice-Daily Exenatide in Basal Insulin–Treated Patients With Type 2 Diabetes. Ann Intern Med. 2011;154(2):103. doi:10.7326/0003-4819-154-2-201101180-00300.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 9.6: Drug review - SGLT2 Inhibitors

SEMDSA Type 2 Diabetes Guideline Expert Committee

None of the SGLT2 inhibitors have been registered in South Africa at the time of publication. The names under which these products will be available in South Africa, if at all, as well as the cost and prescribing limitations, is not known. One or more agents from this class of drug is likely to become available before the next guidelines update. SEMDSA has therefore decided to include guidelines regarding its use. The prescriber is always referred to the product registration label for accurate information before prescribing any drug.

These drugs inhibit the sodium-glucose linked transporter 2 (SGLT2), and the first agent to be approved was dapagliflozin (2011 in Europe). They do not cause hypoglycaemia, are associated with weight loss and empagliflozin has been associated with reduced cardiovascular mortality in selected patients.

9.6.1 Mode of Action[1,2]

SGLT2 in the proximal convoluted tubule is normally responsible for reabsorbing ~90% of the ~180 g of glucose filtered by the kidney each day. This renal glucose reabsorption is increased by 20-40% in type 2 diabetes and contributes to hyperglycaemia. Pharmacological inhibition of SGLT2 inhibits the reabsorption of 30-50% of filtered glucose, resulting in glycosuria of approximately 50-80 g/day. This glucosuric effect helps to ameliorate hyperglycaemia. The increased urinary glucose excretion also results in an ensuing osmotic diuresis (leading to blood pressure and volume reduction) as well as calorie losses of 200 to 300 kcal/day (leading to weight loss). This insulin-independent mode of action is independent of insulin secretion, insulin resistance, stage of disease, race and ethnicity, is associated with low rates of hypoglycaemia and is effective in combination with all other glucose lowering therapies.

9.6.2 Efficacy

Monotherapy

When used as monotherapy in type 2 diabetes, mean placebo adjusted c reductions of 0.6 to 1.2% have been noted.[1–5] A meta-analysis of 45 monotherapy studies involving 11 232 subjects showed a mean placebo adjusted difference of -0.7% in HbA_{1C}.[6] Canagliflozin 300 mg appears to have the greatest efficacy.[7]

Add-on therapy

Add-on to metformin monotherapy[8-13]: *0.5 -1% mean HbA_{1C} reduction.*

Add-on to sulphonylurea monotherapy[14]: -0.7% mean HbA_{1C} reduction

Add-on to metformin and sulphonylurea[15-17]: -0.7 – 0.9%

Add-on to insulin[18-21]: ~ -0.5 to 0.8%

Efficacy in Renal Impairment

The glycaemic efficacy of SGLT2 inhibitors is attenuated in patients with diminished eGFR resulting in modest HbA_{1C} reductions of 0.3 to 0.6%.[22-24] This is presumably because glucose filtration is diminished, and there may be co-existent tubular dysfunction.

Patients with high baseline HbA_{1C}

In a pre-specified pooled analysis of three phase 3 studies, treatment with open-label empagliflozin 25 mg in patients with severe hyperglycaemia (N=184, mean baseline HbA_{1C} 11.15%) resulted in a 3.27% HbA_{1C} reduction at week 24; no placebo was included in these studies.[25]

9.6.3 Microvascular outcomes

There have been no microvascular outcome studies with SGLT2 inhibitors.

9.6.4 Cardiovascular and mortality outcomes

Appendix 9.5 discusses cardiovascular outcome trials (CVOT) mandated by the US FDA.[26] In line with current regulations all three manufacturers of SGLT2 inhibitors have embarked on CVOTs.[26-28] The EMPA-REG OUTCOME study has been completed, and evaluated cardiovascular safety of empagliflozin (versus placebo) in type 2 diabetes patients with established cardiovascular disease. There was ~-0.3% HbA_{1C} difference between the active and placebo arms. There was a statistically significant 14% relative risk reduction for the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in the empagliflozin treated participants after 3.1 years.[27] This was driven mainly by a 38% relative risk reduction in death from cardiovascular causes with no differences in the rates of myocardial infarction or stroke. Analysis of secondary endpoints showed a 35% reduction in hospitalisation for heart failure, and a non-significant increase in stroke and silent myocardial infarction. There was no difference in outcomes between the 10 and 25 mg doses of empagliflozin. The benefits noted occurred early during the course of the study (within three months) and was sustained thereafter, implying that the results were not driven by an effect on atherosclerosis.

The conclusion from this data is that empagliflozin treatment in type 2 diabetes patients with established cardiovascular disease reduces cardiovascular and all cause mortality. The number of patients that would need to be treated to prevent one death was calculated to be 39.

9.6.5 Hypoglycaemia

SGLT2 inhibitors have an insulin-independent mode of action and hypoglycaemia is comparable to placebo except when combined with sulphonylureas or insulin therapy.[1,2,6]

9.6.6 Non-glycaemic benefits

Weight loss

Glucosuria and caloric loss results in a mean weight loss of 1.6 kg to 2.5 kg for different drugs in the class.[7] Weight loss is not dose dependent, is comparable to the weight loss with GLP-1 receptor agonists,[29] and has been durable for two to four years. [11,30]

Blood Pressure

Systematic reviews demonstrate that SGLT2 inhibitors significantly and consistently reduce systolic blood pressure by about 4.0 mmHg, and diastolic blood pressure by about mean -1.6 mmHg from baseline.[31,32] This is presumably due to glucosuria and the ensuing osmotic diuresis. The incidence of orthostatic hypotension was not statistically increased in one systematic review,[31] but was in another.[6] It may be clinically relevant in certain situations (dehydration, elderly, concomitant loop-diuretic use).

Diabetic kidney disease (DKD)22-27,33

SGLT2 inhibitors improve glycaemia and lowers blood pressure. In addition they may attenuate glomerular hyperfiltration independent of blood glucose lowering.[33] Reduction in microalbuminuria has been noted consistently in all studies with SGLT2 inhibitors in DKD.

9.6.7 Adverse Events and Precautions

Common

Mycotic genital infections

Fungal vulvovaginitis and balanoposthitis (infection of the penile glans and foreskin) are the commonest adverse effect of SGLT2 inhibitors. When compared to placebo patients receiving SGLT2 inhibitors are four to six times more likely to develop mycotic infections.[7] Women are twice as likely to be affected.[6,32] These infections apparently respond to over-the-counter antifungal creams or fluconazole 150 mg repeated 48h hours later.[32] SGLT2 inhibitors should be avoided in patients with a history of recurrent yeast infections.

Urinary tract infections (UTI's)

Reports of higher rates of UTI have not been consistent across studies. A recent meta-analysis reported a higher risk of UTI for dapagliflozin but not empagliflozin.[7] The UTI's typically respond to standard antibiotics.

Pyelonephritis and urosepsis (UTI complicated by septicaemia) is rare in clinical trials with SGLT2 inhibitors. However the FDA has drawn attention to 19 post-marketing reports of urosepsis or pyelonephritis.[34] The true incidence of this complication is not known because the FDA has not released comparable figures for patients not taking SGLT2 inhibitor. It is prudent not to prescribe SGLT2 inhibitors to patients with a history of recurrent UTI.

Diuretic effects[6,32]

Polyuria (large urine volume) or pollakiuria (frequent small voids) is common. The pattern of eGFR change with SGLT2 inhibitors has been consistent – an initial decline in GFR (approximately 10%) within the first weeks of therapy (presumably due to diuretic effect and hypovolaemia) - followed by gradual return toward (and sometimes above) baseline over the ensuing weeks to months. This compares favourably to placebo where there is usually a gradual but persistent decline in eGFR. Any sustained reduction in eGFR is fully reversed within three weeks of SGLT2 inhibitor cessation.

Rare but serious

Euglycaemic diabetic ketoacidosis (euDKA)[35]

The incidence of DKA in clinical trial programs involving SGLT2 inhibitors has been estimated to be about 0.1%. There have been rare post-marketing reports from both the US FDA and the European Medicines Agency of cases of DKA associated with SGLT2 inhibitor use.[35] Unlike conventional DKA that is associated with marked hyperglycaemia, the cases with SGLT2 inhibitors typically have blood glucose values below 14.0 mmol/L. This may delay detection, diagnosis and management. Insulin treated patients receiving SGLT2 inhibitors should be warned of the symptoms of DKA and advised to test their urine for ketones whenever these symptoms occur, irrespective of the blood glucose measurement.

Dehydration, hypotension[6,32]

Dehydration is uncommon and may rarely result in acute renal injury.

Hypotension or postural hypotension is also infrequent but may necessitate reduction in anti-hypertensive doses.

It is may be wise to avoid concurrent SGLT2 inhibitor use with loop diuretics.

Malignancy

A numerical imbalance in the number of cases of bladder cancer (0.17% vs 0.03%) has been noted in pooled clinical studies with dapagliflozin. The European Medicines Agency considered the evidence and concluded that a causal relationship was unlikely. Nevertheless dapagliflozin should not be used in patients with a history of bladder cancer, or in combination with pioglitazone, until clarity from the longer-term safety trial with dapagliflozin is published.[26]

Bone fractures

Canagliflozin has been associated with a non-significant increase in the risk of bone fractures in pooled analyses. A prospective study demonstrating a significant reduction in bone mineral density at the hip and lumbar spine in elderly subjects (in part due to weight loss) has led to stronger warning about the potential fracture risk.[36,37]

Acute renal injury

Clinical trials with SGLT2 inhibitors have not demonstrated an increased risk of acute renal injury. However pooled data from regulatory authorities highlight the potential for acute renal injury in patients who become dehydrated or experience hypotension. This is more likely to occur in elderly patients (age >65 years), in patients taking diuretics and in those with stage 2 or 3 chronic kidney disease (eGFR 30 to 60 ml/min).[25,38-40] Acute renal injury is usually reversible with drug cessation and volume correction.

Stroke

There has been a numerical imbalance (not statistically significant) in the number of patients suffering strokes in the EMPA REG OUTCOMES trial as well as pooled analysis of canagliflozin trials.[27,40] This is incongruous with blood pressure lowering data, and its relationship to dehydration and raised haematocrit deserves further study. SGLT 2 inhibitors should not be used in patients at high risk for stroke (uncontrolled blood pressure, significant carotid stenosis, previous history of transient ischaemic attack or stroke).

Lower limb/toe amputations

The CANVAS and CANVAS-R studies have reported a higher rate of lower limb amputations, especially of the toe (8/1000 vs. 4/100 for placebo). The European Medicines agency has added this an adverse event for canagliflozin, and has added a warning on the label for the other two members of the class.[41]

9.6.8 Prescribing information

Each drug has two (2) strengths that have been registered in other countries:

Canagliflozin (Invokana®) 100 mg and 300 mg tablets

Dapagliflozin (Forxiga®) 5 mg and 10 mg tablets

Empagliflozin (Jardiance®) 10 mg and 25 mg tablets.

Dosing

Start with lower dose and increase after three months if metabolic control is not achieved.

Renal dose adjustments

The efficacy of SGLT2 inhibitors is dependent on adequate glomerular filtration. Urinary glucose excretion is about 50% lower in patients with CKD stage 3 (eGFR 30-60 ml/min) treated with SGLT2 inhibitors when compared with those with CKD stage 1 or 2 (eGFR >60 ml/min).[42] The glucose lowering efficacy of these agents in patients with CKD is therefore expected to be attenuated.

Dapagliflozin:

No dose adjustment when eGFR >60 ml/min

Has been studied in CKD stage 3 (eGFR 30-60 ml/min) but failed to demonstrate glycaemic superiority compared to placebo.[24] Dapagliflozin should therefore not be used when the eGFR is <60 ml/min.

Empagliflozin:

No dose adjustment is necessary when eGFR >60 ml/min

Only the higher 25mg dose has been studied in patients with an eGFR <60 ml/min[24]

Contraindicated when eGFR is <45 ml/min

Canagliflozin

No dose adjustment when eGFR is >60 ml/min.

Reduce the dose to 100mg if the patient is already using the drug and the eGFR decreases to 45-59 ml/min, but do not initiate therapy

Contraindicated when eGFR is <45ml/mi

Recommendations

Caveats: Neither the cost nor the exact registered indications for this class are known; these are general recommendations that may change depending on the product registration with the Medicines Control Council of South Africa.

1. Monotherapy when metformin is not tolerated or contraindicated: SGLT2 inhibitors have not been compared directly against metformin in drug naïve patients (they have been studied against placebo). The side-effect profile and need for careful patient selection is a limitation on its use in the primary health care setting. SGLT2 inhibitors are therefore not recommended as monotherapy for type 2 diabetes.
2. Dual therapy as add-on to metformin or other 1st line drugs: SGLT2 inhibitors may be considered for dual therapy in selected patients, based on its glycaemic efficacy, negligible risk of hypoglycaemia and positive effect on weight loss.
3. Triple therapy as add-on to any other 2 oral glucose lowering drugs: SGLT2 inhibitors may be considered for triple therapy in selected patients, based on its glycaemic efficacy, negligible risk of hypoglycaemia and positive effect on weight loss.
4. Add on to insulin: the addition of SGLT2 inhibitors to insulin is not recommended at primary health care level.
5. Established cardiovascular disease: these patients should not be managed at primary health care level. The decision to use SGLT2 inhibitors in this situation should be made by a specialist (physician, cardiologist, endocrinologist).

Author: Aslam Amod
Editors: Zaheer Bayat, Ankia Coetzee, Nazeer A Mohamed, Joel A Dave, Tanya Kinvig and Fraser J Pirie

References

1. Fujita Y, Inagaki N. Renal sodium glucose cotransporter 2 inhibitors as a novel therapeutic approach to treatment of type 2 diabetes: Clinical data and mechanism of action. J Diabetes Investig. 2014;5(3):265-275. doi:10.1111/jdi.12214.
2. Chao EC. SGLT-2 Inhibitors: A New Mechanism for Glycemic Control. Clin Diabetes. 2014;32(1):4-11. doi:10.2337/diaclin.32.1.4.
3. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin Monotherapy in Type 2 Diabetic Patients With Inadequate Glycemic Control by Diet and Exercise. Diabete Care. 2010;33(10):2217-2224. doi:10.2337/dc10-0612.
4. Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised,

double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2013;1(3):208-219. doi:10.1016/S2213-8587(13)70084-6.

5. Stenlöf K, Cefalu WT, Kim K-A, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes, Obes Metab. 2013;15(4):372-382. doi:10.1111/dom.12054.
6. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159(4):262-274. doi:10.7326/0003-4819-159-4-201308200-00007.
7. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes, Obes Metab. 2016;18(8):783-794. doi:10.1111/dom.12670.
8. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013;11(1):43. doi:10.1186/1741-7015-11-43.
9. Häring H-U, Merker L, Seewaldt-Becker E, et al. Empagliflozin as Add-On to Metformin in Patients With Type 2 Diabetes: A 24-Week, Randomized, Double-Blind, Placebo-Controlled Trial. Diabetes Care. 2014;37(6):1650-1659. doi:10.2337/dc13-2105.
10. Nauck MMA, Del Prato S, Meier JJJJJJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin. Diabetes Care. 2011;34(9):2015-2022. doi:10.2337/dc11-0606.
11. Del Prato S, Nauck M, Durán-Garcia S, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. Diabetes, Obes Metab. 2015;17(6):581-590. doi:10.1111/dom.12459.
12. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol. 2014;2(9):691-700. doi:10.1016/S2213-8587(14)70120-2.
13. Cefalu WT, Leiter LA, Yoon K-H, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013;382(9896):941-950. doi:10.1016/S0140-6736(13)60683-2.
14. Strojek K, Yoon K-H, Hruba V, Sugg J, Langkilde AM, Parikh S. Dapagliflozin Added to Glimepiride in Patients with Type 2 Diabetes Mellitus Sustains Glycemic Control and Weight Loss Over 48 Weeks: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial. Diabetes Ther. 2014;5(1):267-283. doi:10.1007/s13300-014-0072-0.
15. Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S, Study 05 Group. Dapagliflozin Improves Glycemic Control and Reduces Body Weight as Add-on Therapy to Metformin Plus Sulfonylurea: A 24-Week Randomized, Double-Blind Clinical Trial. Diabetes Care. 2015;38(3):365-372. doi:10.2337/dc14-0666.
16. Haring H-U, Merker L, Seewaldt-Becker E, et al. Empagliflozin as Add-on to Metformin Plus Sulfonylurea in Patients With Type 2 Diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2013;36(11):3396-3404. doi:10.2337/dc12-2673.
17. Haering H-U, Merker L, Christiansen AV, et al. Empagliflozin as add-on to metformin plus sulphonylurea in patients with type 2 diabetes. Diabetes Res Clin Pract. 2015;110(1):82-90. doi:10.1016/j.diabres.2015.05.044.
18. Wilding JPH, Woo V, Rohwedder K, Sugg J, Parikh S. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: Efficacy and safety over 2 years. Diabetes, Obes Metab. 2014;16(2):124-136. doi:10.1111/dom.12187.
19. Rosenstock J, Jelaska A, Zeller C, Kim G, Broedl UC, Woerle HJ. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. Diabetes, Obes Metab. 2015;17(10):936-948. doi:10.1111/dom.12503.
20. Rosenstock J, Jelaska A, Frappin G, et al. Improved Glucose Control With Weight Loss, Lower Insulin Doses, and No Increased Hypoglycemia With Empagliflozin Added to Titrated Multiple Daily Injections of Insulin in Obese Inadequately Controlled Type 2 Diabetes. Diabetes Care. 2014;37(7):1815-1823. doi:10.2337/dc13-3055.
21. Neal B, Perkovic V, Matthews DR, et al. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): A randomized, placebo-controlled trial. Diabetes, Obes Metab. 2017;19(3):387-393. doi:10.1111/dom.12829.
22. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int. 2014;85(4):962-971. doi:10.1038/ki.2013.356.
23. Yale J-F, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes, Obes Metab. 2013;15(5):463-473. doi:10.1111/dom.12090.
24. Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014;2(5):369-384. doi:10.1016/S2213-8587(13)70208-0.
25. European Medicines Agency. Jardiance : European Public Assessment Report - Product Information. Updated 07 December 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002677/WC500168592.pdf. Accessed February 10, 2016.
26. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT01730534. Accessed February 15, 2016.
27. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720.
28. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)—A randomized placebo-controlled trial. Am Heart J. 2013;166(2):217-223.e11. doi:10.1016/j.ahj.2013.05.007.
29. Lorenzi M, Ploug UJ, Langer J, Skovgaard R, Zoratti M, Jansen J. Liraglutide Versus SGLT-2 Inhibitors in People with Type 2 Diabetes: A Network Meta-Analysis. Diabetes Ther. 2017;8(1):85-99. doi:10.1007/s13300-016-0217-4.
30. Leiter LA, Yoon K-H, Arias P, et al. Canagliflozin Provides Durable Glycemic Improvements and Body Weight Reduction Over 104 Weeks Versus Glimepiride in Patients With Type 2 Diabetes on Metformin: A Randomized, Double-Blind, Phase 3 Study. Diabetes Care. 2015;38(3):355-364. doi:10.2337/dc13-2762.
31. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: A systematic review and meta-analysis. J Am Soc Hypertens. 2014;8(4):262-275. doi:10.1016/j.jash.2014.01.007.
32. Schwartz SS, Ahmed I. Sodium-Glucose Cotransporter-2 Inhibitors: An Evidence-Based Practice Approach to Their Use in the Natural History of Type 2 Diabetes. Curr Med Res Opin. February 2016:1-43. doi:10.1185/03007995.2016.1151774.
33. De Nicola L, Gabbai FB, Liberti ME, Sagliocca A, Conte G, Minutolo R. Sodium/Glucose Cotransporter 2 Inhibitors and Prevention of Diabetic Nephropathy: Targeting the Renal Tubule in Diabetes. Am J Kidney Dis. 2014;64(1):16-24. doi:10.1053/j.ajkd.2014.02.010.
34. U.S. Food and Drug Administration. Safety Alerts for Human Medical Products - SGLT2 Inhibitors: Drug Safety Communication - Labels to Include Warnings About Too Much Acid in the Blood and Serious Urinary Tract Infections.
35. Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis : A Predictable , Detectable , and Preventable Safety Concern With SGLT2 Inhibitors. Diabetes Care. 2015;38(September):1638-1642. doi:10.2337/dc15-1380.
36. FDA. Invokana and Invokamet (canagliflozin): Drug Safety Communication - New Information on Bone Fracture Risk and Decreased Bone Mineral Density. 10 September 2015. http://www.fda.gov/Drugs/DrugSafety/ucm461449.htm. Accessed February 21, 2016.
37. Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin. J Clin Endocrinol Metab. 2016;101(1):44-51. doi:10.1210/jc.2015-1860.
38. FDA Briefing Document NDA 202293. Dapagliflozin Oral Tablets, 5 and 10 mg. Sponsor : Bristol-Myers Squibb Advisory Committee Meeting December 12, 2013. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM378076.pdf. Accessed February 20, 2016.
39. European Medicines Agency. Forxiga : European Public Assessment Report - Product Information. Updated 08 May 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002322/WC500136026.pdf. Accessed February 10, 2016.

40. European Medicines Agency. Invokana : European Public Assessment Report - Product Information. Updated 13 January 2016. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002649/WC500156456.pdf. Accessed February 10, 2016.
41. European Medicines Association. EMA Adds Potential for Toe Amputation to SGLT2 Inhibitor Prescribing Info | RAPS. February 2017. http://www.raps.org/Regulatory-Focus/News/2017/02/24/26961/EMA-Adds-Potential-for-Toe-Amputation-to-SGLT2-Inhibitor-Prescribing-Info/. Accessed February 20, 2017.
42. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-Glucose Cotransport Inhibition With Dapagliflozin in Type 2 Diabetes. Diabetes Care. 2009;32(4):650-657. doi:10.2337/dc08-1863.

Bibliography

1. Goring S, Hawkins N, Wygant G, et al. Dapagliflozin compared with other oral anti-diabetes treatments when added to metformin monotherapy: A systematic review and network meta-analysis. Diabetes, Obes Metab. 2014;16(5):433-442. doi:10.1111/dom.12239.
2. Yang X-P, Lai D, Zhong X-Y, Shen H-P, Huang Y-L. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. Eur J Clin Pharmacol. 2014;70(10):1149-1158. doi:10.1007/s00228-014-1730-x.
3. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes. JAMA. 2016;316(3):313. doi:10.1001/jama.2016.9400.
4. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-412. doi:10.1136/bmj.321.7258.405.
5. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2008;358(24):2560-2572. doi:10.1056/NEJMoa0802987.
6. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care. 2000;23 Suppl 2:B21-9.
7. Rizvi A, Hartaigh B ó., Knaapen P, et al. Rationale and Design of the CREDENCE Trial: computed TomogRaphic evaluation of atherosclerotic DEtermiNants of myocardial IsChEmia. BMC Cardiovasc Disord. 2016;16(1):190. doi:10.1186/s12872-016-0360-x.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 9.7: Alpha glucosidase inhibitors (Acarbose)

SEMDSA Type 2 Diabetes Guideline Expert Committee

9.7.1 Mechanism of action

Acarbose is an oligosaccaride that competitively inhibits alpha glucosidase on the brush border of the small intestine. This inhibits the conversion of complex carbohydrates into monosaccharides, and results in a reduction and delay in the absorption of glucose. The nett effect is a decrease in post prandial plasma glucose.

9. 7.2 Efficacy[1,2]

In a meta-analysis of 30 randomised controlled trials, Acarbose monotherapy reduced HbA_{1C} by 0.8% without causing hypoglycaemia or weight gain. The dose of 100 mg three times daily was not more effective than addition to metformin, sulphonylurea and insulin, which resulted in HbA_{1C} reductions of 0.8%, 0.9% and 0.5%, respectively. In all studies, Acarbose significantly reduced postprandial glucose (2.3-3.5 mmol/l), and caused statistically significant weight loss or was weight neutral.

The Gluco VIP[3] observational study of 15,034 patients showed a mean two hour PPG decreased by 4 mmol/l and a mean HbA_{1C} reduction of 1.1%.

9.7.3 Cardiovascular effects

The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM)[4] trial randomly assigned 1 429 patients with impaired glucose tolerance to Acarbose 100 mg three times daily or placebo for a mean of 3.3 years. In a pre-planned secondary analysis, Acarbose significantly reduced the risk of cardiovascular events by 49%, and the risk of developing hypertension was decreased by 34%. The magnitude of the effect is unexpected and may be related to the fact that Acarbose targets postprandial hyperglycaemia (an independent risk factor for cardiovascular disease), but it needs verification. However, positive cardiovascular outcomes trials have been difficult to achieve, and these results should not be ignored.

ACE (Acarbose Cardiovascular Evaluation) Trial[5] is a four year, multi-centre, double-blind, randomised parallel-group trial to determine whether reducing post-prandial glycaemia with Acarbose can reduce cardiovascular-related morbidity in patients with established coronary heart disease or acute coronary syndrome who have impaired glucose tolerance. Primary Outcome is occurrence of any of the following; Cardiovascular death, Non-fatal MI, Non-fatal stroke [Time Frame: 7 500 patients followed-up for approximately four years until 904 adjudicated Primary Outcome Measures have been recorded]. Trial is due to report results in 2018.

9.7.4 Dosing

Start with 50 mg once daily with meals, and increase by 50 mg every two weeks if tolerated. The maximum dose is 100 mg three times daily, although a meta-analysis showed the same glycaemic benefit and better tolerability with 50 mg three times daily. Not recommended for use in eGFR <30 ml/min.

9.7.5 Adverse effects

At higher doses, Acarbose may give rise to transient elevation of hepatic transaminases. Patients up titrated to maximum dose should be closely monitored for the first 6 months. If elevated transaminases are observed a reduction in dosage is warranted. If elevated transaminase levels persist, then withdrawal of therapy may be warranted.

Acarbose does not cause hypoglycaemia when used as monotherapy, but may aggravate hypoglycaemia caused by sulphonylureas and insulin.

Gastrointestinal side-effects (flatulence and diarrhoea) are common when initiating therapy, and are related to fermentation of the high saccharide load in the colon. This has led to discontinuation rates as high as 35% in clinical trials. Side-effects can be minimised by slow dose titration.

During the Gluco VIP Study[3] conducted in 15 countries/regions in which 15,661 patients were considered valid for safety analysis, drug tolerability was rated as 'very good' or 'good' in 84.9 % of patients. Drug-related adverse events, mainly gastrointestinal, were reported in 490/15 661 patients (3.13 %). The investigators concluded that Acarbose is safe and well tolerated in a large cohort of Asian patients with type 2 diabetes.

9.7.6 Pregnancy

Safety and Efficacy has not been established – Category B

Author: Zaheer Bayat

References

1. Van de Laar FA, Lucassen PL, Akkermans RP, et al. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev(2). 2005:CD003639.
2. Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. Ann Intern Med. 1994;121(12):928.
3. Chiasson JL, Josse RG, Gomis R, et al. STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003;290(4):486.
4. Acarbose Cardiovascular Evaluation Trail. https://www.dtu.ox.ac.uk/ace/. Accessed 24th February 2016
5. Zhang W, Kim D, Philip E, et al. A multinational, observational study to investigate the efficacy, safety and tolerability of acarbose as add-on or monotherapy in a range of patients: the Gluco VIP study. Clin Drug Investig. 2013: 33(4):263-74.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 10.1 Drug Review: Insulin

SEMDSA Type 2 Diabetes Guideline Expert Committee

Also refer to: Appendix 10.2, 10.3 and Chapters 10 and 11.

The discovery of insulin in 1921 by Banting and Best was one of the most dramatic and important milestones in medicine. Insulin is life saving in type 1 diabetes where it is essential for survival. However, its greatest utility today is in type 2 diabetes when it is needed for glycaemic control.

10.1 Introduction

Although insulin resistance is a key component in the pathophysiology of type 2 diabetes, with time declining beta cell dysfunction results in many patients requiring insulin therapy to maintain optimal glycaemic control. Despite the well-established benefits of optimal glycaemic control, there exists a great deal of inertia to initiating insulin therapy, both on the part of clinicians and patients [the other type of "insulin resistance"]. Some of the factors preventing insulin initiation include concerns of hypoglycaemia, weight gain, fear of injections and complexity of insulin self-management. As a result, there are delays of up to seven years in treatment intensification despite suboptimal glycaemic control on two or three oral glucose lowering drugs.[1,2] On the other hand, insulin may sometimes initiated too early when glycaemic control could just as easily be achieved with less expensive and less complex oral therapies, with fewer side-effects. Glycaemic control is the key factor, as there is no evidence to suggest that achieving glycaemic control with insulin *per se*, is more beneficial than achieving the same level of control with any other agent. However, in some patients with type 2 diabetes, due to significant beta-cell failure, only the use of insulin will be enable them to achieve their individualised HbA_{1C} target.

Since the introduction of human insulin in the 1980's there has been significant development in this therapeutic area. A large number of options in insulin therapy now exist including human regular and intermediate insulins, rapid-acting and basal insulin analogues, newer ultra-long-acting and concentrated [U300] basal analogues, and various mixes. This chapter will review the issues pertinent to insulin use in the primary healthcare setting i.e.:

a. What are the available insulin preparations?

b. Which insulins are suitable for use in type 2 diabetes?

c. When should insulin be initiated?

d. How should insulin be initiated and prescribed?

Complex insulin regimens will not be discussed.

10.2 What are the available insulin preparations and how are they classified?

Table I explains the terminology used in classifying insulins, and Table II is a description of the time-action profiles for insulin

Table I: Insulin terminology and classification

By production source	Animal insulin	Extracted from pig or cows (porcine or bovine).
	rDNA insulin	Synthesised using recombinant DNA technology.
Similarity with human insulin	Human insulins	Have the identical amino acid sequence and physico-chemical properties as native human insulin.
	Analogue insulins	Are insulins that do not exist in nature; their amino acid sequence and/or physico-chemical properties have been altered. These changes can be used to speed up the absorption and action of insulin (rapid-acting analogues), or delay its absorption and prolong its action (long-acting analogues).
By insulin concentration:	U100 insulins	This is the number of units of insulin in each millilitre (ml) of the insulin solution. U100 insulin contains 100u/ml.
	U300 insulins	U300 insulin contains 300u/ml.
By onset of action	Short acting	Regular human insulins (identical to human insulin but in a soluble solution) are absorbed within ½ hour and have a peak action within 3.5 hours. This is called short acting insulin.
	Intermediate and long-acting insulins	Other insulins are classified relative to regular insulin. Intermediate-acting human insulins have a slower absorption and longer duration of action by adding protamine (NPH) or excess zinc ions (Lente). Some analogue insulins have been altered to either be faster acting than regular insulin (rapid-acting analogues), or to prolong its action (long-acting or ultra long-acting analogues.
By the timing of the insulin needed in relation to meals:	Prandial (mealtime or bolus) insulin	This is insulin delivered with the aim of regulating the rapid blood glucose rise after meals. This can be accomplished with either short or rapid acting insulin injected before the meal.
	Basal insulin	Insulin requirements in the post-absorptive and fasting state e.g. overnight, is called basal insulin; the amount required per hour is smaller and needs to be more consistent to regulate hepatic glucose production, which is the main glucose source in the fasting state.

Table II: Time-action profiles of insulins

Type [*proprietary name*]	**Onset**	**Peak**	**Duration**
Short-acting regular human insulins [*Actrapid, Humulin-R, Insuman, Biosulin-R*]	30-60 minutes	2-3 hours	Up to 7-8 hours
Rapid-acting analogue insulins Aspart [*NovoRapid*] Glulisine [*Apidra*] Lispro [*Humalog*]	5-15 minutes	1.5-3.5 hours	5-8 hours
Intermediate-acting (basal) human insulins			
NPH - neutral protamine Hagedorn [*Humulin-N, Protaphane, Biosulin-N*]	120-240 minutes	4-10 hours	10-18 hours[§]
Lente – contains zinc [*Biosulin-L*]	90 minutes	4-8 hours	22-24 hours[§]
Long-acting (basal) analogue insulins Glargine [*Lantus, Optisulin, Basaglar*]	120-240 minutes	No peak	Up to 24 hours[§]
Pre-mixed human (biphasic) insulins 30% Regular + 70% NPH [*Actraphane, Humulin 30/70, Insuman, Biosulin 30/70*]	30-60 minutes	Dual peak	10-18 hours
Pre-mixed analogue insulins	5-15 minutes	Dual peak	10-16 hours
Rapid-acting plus basal Biphasic aspart [NovoMix] Biphasic lispro [Humalog Mix25, Humalog Mix50]			
Rapid-acting plus ultra-long-acting basal Pre-mixed aspart/degludec [Ryzodeg]	5-15 minutes	Dual peak	>24 hours

[§]The duration of action of intermediate and long acting insulins is dose dependent. For example, the duration of action of insulin detemir 0.2u/kg and 0.4u/kg is 12 and 20 hours respectively.[3] At lower doses, basal insulin may need to be dosed twice daily depending on individual patient responses.

preparations available in South Africa. Appendix 10.2 shows the cost of these insulin preparations in the private-health sector.

10.3 Which insulins to use?

10.3.1 Human insulins vs. analogue insulins

For each instance of insulin use, the practitioner and patient is faced with a choice of opting for a human insulin or an analogue insulin. This section describes some clinical trial evidence to guide the rational use of insulin in the treatment of type 2 diabetes.

Rapid-acting analogues vs. short-acting regular human insulin

All 3 currently available rapid-acting analogue insulins (lispro, glulisine, aspart) have been compared to regular human insulins as part of basal bolus therapy in patients with T2DM.[4–6] In addition, there have been a number of meta-analyses of trials comparing rapid-acting insulin analogues and short-acting regular human insulin (Appendix 10.3).[7–11] In summary, these meta-analyses showed that HbA_{1C} reductions with rapid acting-analogues and regular human insulin were similar, while post-prandial glucose control with analogues was found to be superior. There was no difference in the incidence of hypoglycaemia. The rapid-acting analogues have the benefit of a rapid onset of action, making it convenient to inject just prior to eating (as opposed to injecting 30 minutes before eating for human insulin).

Recommendations: Rapid-acting insulin analogues are preferred to short-acting human insulins, for improved convenience and for post-prandial glucose control, when the cost is not prohibitive.

Basal insulin analogues vs. human basal insulin (NPH)

Two separate systematic reviews have compared the outcomes of treatment with NPH insulin and basal insulin analogues.[12,13] In summary, these reviews showed similar HbA_{1C} reduction when using either type of insulin with no difference in long-term outcomes including morbidity and mortality. However, there were lower rates of symptomatic and nocturnal hypoglycaemia with basal insulin analogues. Insulin detemir has also been shown to have a weight advantage compared with NPH and insulin glargine.[13] In summary, long-acting basal insulin analogues do not offer better glycaemic control when compared to human basal insulins. Although the rates of severe hypoglycaemia are not lower, long-acting analogue insulins are less likely to cause nocturnal hypoglycaemia when compared with human basal insulins.

Recommendations: Since human basal insulins are historically less expensive than analogue insulins it is cost-effective to initiate basal insulin therapy with a human basal insulin, except when the risk of hypoglycaemia is unacceptably high (see Chapter 11). Patients with subsequent recurrent nocturnal hypoglycaemia should then be switched to an analogue basal insulin. When the cost

differential between human basal and analogue insulins is not great, initial treatment with an analogue basal insulin is preferred.

10.3.2 Biosimilar insulins vs. originator insulins

Definition of biosimilars, clones and generics

As opposed to simple chemical drugs that are usually small molecules produced synthetically, biological agents such as insulin are produced by complex means using microorganisms, cell or tissue culture. *Generics* of small molecules, due to their relative simplicity, are produced identically to the originator with only evidence of similar bioavailability required by regulatory bodies. Biological agents are large complicated molecules with equally complicated production protocols that remain the proprietary information of the original manufacturer after expiry of the molecule's patent. Therefore, a *biosimilar*, while intended to have the same clinical effect as the originator, is produced by different means to the originator. As minor changes to a complex molecule could impact on efficacy and safety, regulatory authorities require head-to-head comparison with the originator in the registration of a biosimilar. This is likely to impact on the cost benefits of biosimilars compared with generics.[14] A *clone* is identical to the originator in every detail and often produced by the same manufacturer. In South Africa, insulin glargine, a basal insulin analogue, is available as a clone (Optisulin®) and a biosimilar (LY Iglarg or Basaglar®).

Biosimilar insulins in South Africa

This biosimilar insulin glargine has been evaluated in comparison to the originator in terms of efficacy and safety in patients with type 1 and type 2 diabetes mellitus. The Element 1 study was a phase 3, randomized, 52 week trial in patients with type 1 diabetes, and will not be discussed in this guideline.[15] In the Element-2 study, patients with type 2 diabetes on up to 2 oral agents were randomized to LY Iglarg or originator insulin glargine for 24 weeks.[16] LY Iglarg was non-inferior to insulin glargine for change in HbA_{1C} from baseline. Adverse events, allergic reactions, weight change, hypoglycaemia and insulin antibodies were similar between treatment groups.

A biosimilar human 30/70 premix insulin (Biosulin 30/70®) has also been compared to originator premix human insulin, and demonstrated equivalent glycaemic control and safety.[17]

Recommendations Currently in South Africa we have access to 3 preparations of insulin glargine (originator, clone and biosimilar). There are also biosimilar insulins for human short-acting, intermediate-acting and premix insulins. These are all registered with the Medicines Control Council. Based on current evidence, the efficacy and safety profiles of these preparations are similar. While it is not recommended that patients with stable glycaemic control be unnecessarily switched to an alternative preparation, if needed, this should be done on a dose for dose basis. When treatment with human or analogue insulin is initiated, the insulin with the lowest acquisition cost within the class is preferred.

10.4 When should insulin be initiated?

10.4.1 The evidence base for insulin therapy

The question often arises – should insulin be initiated early in the course of type 2 diabetes for some or other perceived benefit, even when glycaemic control is achievable with other therapies, or should insulin be delayed for as long as possible because of possible harms. Two randomised controlled clinical trials have examined the question regarding early insulin therapy.[18,19] These and other studies are discussed below.

a. United Kingdom Prospective Diabetes Study (UKPDS)[18]

The 10-year follow-up of the UKPDS showed that newly diagnosed patients with type 2 diabetes that were randomised to receive intensive treatment with a sulphonylurea (SU) or insulin had similar relative reductions in risk for microvascular disease. Initial treatment with insulin in newly diagnosed patients was not superior to SU for any outcomes. However, insulin treated patients gained significantly more weight and had a significantly higher rate of hypoglycaemia.[18] Insulin was not superior to diet / conventional therapy (where patients were only treated when the fasting plasma glucose exceeded 15mmol/L) for macrovascular and mortality outcomes. In an observational study, 10 years after the trial had completed, both early insulin and SU treatment was equally associated with lower rates of any diabetes-related end-point (9%, P = 0.04), microvascular disease (24%, P = 0.001), myocardial infarction (15%, P=0.01) and death from any cause (13%, P = 0.007) when compared to conventional treatment.[20]

Unfortunately, these trials (UKPDS) were not designed to study the safety of one drug against another. In the UKPDS 34 study, for example, metformin reduced macrovascular events and mortality in obese patients whereas insulin did not.[21] However, because of the trial design, it is not possible to determine whether the different outcomes were due to an improved safety of metformin, or a potential harm of insulin therapy. The conclusion is that improving glycaemic control with insulin reduces microvascular complications to the same extent as sulphonylureas, compared to placebo, and that insulin therapy should be initiated whenever glycaemic control is not possible with other glucose lowering drugs.

b. Outcome Reduction with an Initial Glargine Intervention Trial (ORIGIN)[19]

The ORIGIN trial tested the hypothesis that normalization of fasting plasma glucose with basal insulin would reduce cardiovascular disease in patients with diabetes and intermediate dysglycaemia, as well as prevent the progression of IFG/IGT to diabetes. The trial showed no reduction in cardiovascular disease in patients treated with insulin glargine for a median duration of 6 years. Patients with intermediate dysglycaemia treated with basal insulin were 28% less likely to develop diabetes compared with controls but at the cost of weight gain and increased hypoglycaemia. There was no increased risk of cancer

associated with insulin glargine in this trial (insulin dose range 0.19 to 0.53u/kg; duration 6 years). A meta-analysis of insulin studies confirmed that insulin had no benefit over placebo/diet on mortality or cardiovascular outcomes (similar to UKPDS and the ORIGIN studies).[22]

These trials show that initiating insulin therapy early, when glycaemic control is not poor, carries no particular benefit over other agents, but does increase hypoglycaemia and causes weight gain.[22]

c. Other safety studies

Observational studies have reported an increased cardiovascular and mortality risk with insulin therapy when compared to other therapies.[23–26] However, observational data do not allow causal inferences. Insulin therapy has also been associated with worse outcomes in patients with pre-existing cardiovascular disease in the DIGAMI 2 and BARI-2D trials.[27,28] A network meta-analysis of mainly short-term randomised controlled trials reported no differences in the cardiovascular safety for any of the available anti-diabetic therapies.[29]

d. Efficacy studies

In the meta-analysis by Liu et al., basal insulin added to metformin as a 2nd line agent resulted in similar HbA_{1C} reductions to SUs and thiazolidinediones (TZDs) (~0.85%), and was less than GLP-1 receptor agonists (GLP-1RAs) and biphasic insulin.[30] Weight gain was not statistically different between the three treatments (SU, TZD and basal insulin), and hypoglycaemia was significantly lower with TZDs.

In the meta-analysis by McIntosh et al., basal or biphasic insulin added as a 3rd anti-diabetic agent to metformin and SU lowered HbA_{1C} by 1.17%, and was not statistically different to the reductions with TZDs (0.96%), DPP-4 inhibitors (0.89%) or GLP-1RAs (0.96%).[31] Insulin and TZDs were associated with weight gain, DPP-4 inhibitors were neutral and GLP-1RAs were associated with weight loss.[31]

In the meta-analysis by Palmer et al., all drug classes were equally efficacious compared to insulin, when added to metformin as a 2nd line anti-diabetic agent.[29] For 3rd line therapy (added to metformin + SU), TZD and basal insulin were equally efficacious with similar weight gain and hypoglycaemia.[29] Insulin treatment was associated with the lowest odds of treatment failure. Insulin and TZDs were more effective than DPP-4 inhibitors for lowering HbA_{1C} and also for avoiding treatment failure.[29]

The Treating to Target in Type 2 Diabetes (4-T) Study compared 3 insulin regimens in patients with suboptimal glycaemic control, who were taking oral agents (metformin and SU).[32] The three-year follow-up of the 4-T study showed that median HbA_{1C} levels were similar for patients receiving biphasic insulin aspart (7.1%), prandial insulin aspart (6.8%), and basal insulin detemir (6.9%) insulin-based regimens. However, the median rates of hypoglycaemia per 100 patients per year were lowest in the basal group (170 episodes), higher in the biphasic group (300 episodes), and highest in the prandial group (570 episodes). In addition, the mean weight gain was higher in the prandial group than in either the biphasic or the basal groups. Other adverse event rates were similar in the three groups. This trial provides a sound basis for the recommendation that if insulin therapy is considered as the 3rd line option of treatment, it should be initiated using a basal insulin regimen i.e. adding an intermediate or long-acting insulin at bedtime.

Caution is advised in interpreting the above meta-analyses and studies in the South African context, as the data on SUs in the meta-analyses refer mainly to glibenclamide and glimepiride (which have higher rates of hypoglycaemia and weight gain compared to gliclazide), and also because the data on basal insulins is based largely on analogue insulin use, which have lower rates of hypoglycaemia and weight gain (in the case of insulin detemir) than NPH insulins.

d. Evidence-based recommendations for insulin in type 2 diabetes

The current evidence for insulin therapy is as follows:

1. Intensive glycaemic control with insulin therapy reduces microvascular complications.[18]
2. There is no evidence that insulin therapy is associated with better outcomes or particular advantages, when compared to other therapies that can achieve similar glycaemic control[18,19,27,28]
3. There is inconclusive evidence to suggest that insulin therapy may be associated with worse cardiovascular and mortality outcomes when compared to other therapies that can achieve similar glycaemic control.[21,23–28]
4. In stable patients without metabolic decompensation, insulin treatment should be initiated with a basal insulin.[32]
5. In multiple analyses, basal insulin is not more effective than other anti-diabetic agents in lowering HbA_{1C}.[29–31] Additionally, it is a complex treatment requiring additional resources for education and titration. Insulin is therefore not recommended as a 2nd line anti-diabetic agent in stable patients, and should be one of the options available as a 3rd line anti-diabetic agent.

10.4.2 Indications to initiate insulin:

The indications for insulin treatment in non-pregnant adults are:

1. At diagnosis, or at any stage of type 2 diabetes, when there is metabolic decompensation with any of the following features:

    Catabolism (marked weight loss)

    Fasting plasma glucose levels >14 mmol/l

    Random glucose levels consistently > 16.5 mmol/l

    HbA_{1C} > 10%

    Presence of persistent ketogenesis, ketoacidosis or hyperosmolar non-ketotic state

The management of this category of patient is not the subject of this guideline; these patients should be managed intensively, either with a basal-bolus or premix insulin regimen, and specialist referral is recommended.

2. For stable patients without metabolic decompensation, insulin should be considered as a treatment option when glycaemic control is not achieved or maintained with 2 or more other anti-diabetic agents.

10.5 How should insulin therapy be initiated?

The numerous insulin preparations and combinations can make insulin therapy complicated and confusing for the primary care practitioner. **The following recommendations can be made to simplify decision-making (based on the discussion above):**

1. Consider the addition of insulin to an existing 2-drug regimen when glycaemic targets are no longer met. Other options will include adding a 3rd oral anti-diabetic agent or a GLP-1 receptor agonist. Refer to Chapter 11 for guidance on choosing the most appropriate 3rd anti-diabetic agent.
2. When adding insulin as a 3rd anti-diabetic agent, the choice of insulin regimen should be a once daily basal insulin regimen to minimise hypoglycaemia and weight gain.
3. Choose insulins with a low acquisition cost. There are no substantial differences within a particular class of insulins to justify large differences in cost. Biosimilar insulins and clones are acceptable. If costs are similar, a basal insulin analogue is preferred to human insulin. When the cost-differential is high, start with a human basal insulin.
4. If nocturnal hypoglycaemia is a limiting factor to achieving glycaemic control with a human basal insulin, switch to a long-acting basal insulin analogue (if not already in use).
5. When glycaemic control deteriorates with a 3-drug regimen that includes an adequately titrated basal insulin, treatment should be escalated to either a premix insulin regimen, or a "basal plus" regimen (where the basal insulin is maintained and prandial doses of short acting insulin is added). A third alternative would be the addition of a GLP-1 receptor agonist to the basal insulin regimen. Refer to Chapter 11 for further guidance.
6. When glycaemic control deteriorates with a triple oral regimen (e.g. metformin + SU + TZD/DPP-4 inhibitor/SGLT2 inhibitor), continue metformin treatment and initiate insulin treatment with a twice-daily premix insulin, or refer the patient for basal-bolus insulin therapy.
7. Use only insulin pen delivery devices (disposable pens or pen refills); vials and syringes should not be used.

Prior to initiating insulin treatment, it is important to ensure that there are adequate resources avaiable to support the patient in initiating and adjusting insulin treatment. Note that in the 4T study discussed above, 28% and 63% of patients achieved an HbA_{1C} <7% at 1 year and 3 years respectively.[32,33] To achieve this result, patients had to be willing to perform self-blood glucose monitoring, they had access to dietitians and diabetes educators, they had clinic visits at weeks 0, 2, 6, 12, 24, 38 and 52 weeks (7 face-to-face visits within a year), and frequent interim telephonic contact and support. For the latter 2 years of the study, clinic visits occurred every 12 weeks, again with interim telephonic contact. Before each clinic or telephone contact, patients were required to perform pre-breakfast and pre-supper SBGM for 3 consecutive days. In addition they performed an 8-point glucose profile (including 3am) at week 0, 12, 24, 38 and 52, and also tested blood glucose whenever they felt unwell. Glucose test-strip supply was unlimited and uninterrupted. A computer system guided insulin dose titration and also monitored investigator and patient compliance with the monitoring and titration protocol. The target fasting glucose was 4.0 to 5.5 mmol/L and the post-prandial glucose target was 5.0 to 7.0 mmol/L.

This type of protocol for insulin therapy is commonplace, and some trials have used even more rigorous SBGM and titration algorithms. An inability to offer similar support services and "forced" titration protocols to patients when initiating insulin therapy is unlikely to achieve similar results to that seen in clinical trials, and is likely to result in treatment failure.

10.5.1 Initiating and titrating basal insulin as a 3rd anti-diabetic agent (refer to chapter 11, figure 2)

1. Ensure that there are adequate resources avaiable to support the patient in initiating and adjusting insulin treatment: protocols for monitoring and titration, regular access to a diabetes nurse educator to be instructed on injection technique, SBGM, management of hypoglycaemia, hyperglycaemia and sick-days, access to frequent doctor and clinic visits (6 per year), telephonic support between visits, uninterrupted supply of insulin and glucose test strips.
2. Continue all oral agents.
3. Initiate 10 units of basal insulin (or 0.2u/kg) using an intermediate or long-acting insulin (use insulins with a low acquisition cost; clones and biosimilar insulins are acceptable).
4. Titrate dose as described in Chapter 11, Figure IV
5. If unexplained nocturnal hypoglycaemia occurs, instruct the patient to reduce the basal insulin dose by 10% or 2-4 units, to stop titration, and to inform the doctor if it occurs again. If there are persistent episodes of nocturnal hypoglycaemia then switch to a long-acting insulin analogue (if not already in use).
6. Consider using a long-acting insulin analogue (glargine, detemir) in the following situations:
   - If nocturnal hypoglycaemia is problematic with NPH insulin
   - In those who require assistance from a carer or healthcare professional to administer their insulin injections
   - In those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes
   - When circumstances exist where the risk of severe hypoglycaemia and/or its potential consequences can be significant and/or catastrophic (Refer to Chapters 11 and 12)

10.5.2 Escalating to pre-mixed insulin (refer to chapter 11, figure 3)

1. Ensure that there are adequate resources avaiable to support the patient in initiating and adjusting insulin treatment: protocols for monitoring and titration, regular access to a diabetes nurse educator to be instructed on injection technique, SBGM, management of hypoglycaemia, hyperglycaemia and sick-days, access to frequent doctor and

clinic visits (6 per year), telephonic support between visits, uninterrupted supply of insulin and glucose test strips.

2. Continue with metformin only and stop all other anti-diabetic drugs.
3. Insulin dose:
   a. Split the existing basal insulin dose to give 2/3 as a premix in the morning before breakfast and 1/3 as a premix in the evening before supper
   b. If the patient is not already on a basal insulin (e.g. a patient on 3 oral drugs, or 2 oral drugs and a GLP-1RA), then initiate premix insulin at a total dose of 0.3 u/kg given as 2/3 in the morning before breakfast and 1/3 in the evening before supper. Use premixes with a low acquisition cost.
4. The patient must monitor his or her fingerprick glucose before breakfast and before supper. The target glucose will vary depending on the individualised target HbA_{1C} (Refer to Chapter 8)
5. Titrate the pre-breakfast insulin dose to achieve the pre-supper target glucose level, and vice versa.
6. Titration increments can be calculated using Figure IV in Chapter 11. Titration frequency varies, depending on circumstances. For example, titration may take place daily if the patient is under direct supervision in hospital, weekly if the patient needs to see the healthcare provider to supervise titration as an out-patient, or every three days if the patient has good numeracy skills and is able to self-titrate without supervision.
7. If unexplained hypoglycaemia occurs, instruct the patient to reduce the last injected insulin dose (preceding the hypoglycaemic event) by 10% and to stop titration. If the patient experiences recurrent episodes of hypoglycaemia then they should contact their doctor, who could then consider an analogue insulin pre-mix (if not already in use) or refer to a specialist.

10.5.3 Escalating from basal insulin to a "basal-plus" insulin regimen (refer to chapter 11, figures 2 and 3)

Patients suboptimally controlled with an existing basal insulin regimen may improve their glycaemic control by targeting post-prandial hyperglycaemia. A short or rapid-acting insulin can be added befor the largest meal of the day, or before the meal that has the greatest post-prandial glucose excursion. This short/rapid acting insulin can then be titrated based on the SBGM level before the next meal (refer to Chapter 11, Figures IV and V). Further doses of short or rapid acting insulin can be progressively added for the other meals that are associated with post-prandial hyperglycaemia, until a complete basal-bolus regimen is used. Oral agents other than metformin should be progressively discontinued to reduce the complexity of the regimen.

Authors: Aslam Amod, Joel Dave and Zane Stevens

References

1. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical Inertia in People With Type 2 Diabetes. Diabetes Care. 2013.
2. Khunti S, Davies MJ, Khunti K. Clinical inertia in the management of type 2 diabetes mellitus: a focused literature review. Br J Diabetes. 2015;15(2):65. doi:10.15277/bjdvd.2015.019.
3. Levemir® (insulin detemir) [product monograph]. Novo Nordisk Canada Inc., Ontario, Canada. 2016.
4. Ross SA, Zinman B, Campos R V, Strack T, Canadian Lispro Study Group. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. Clin Investig Med. 2001;24(6):292-298.
5. Bretzel RG, Arnolds S, Medding J, Linn T. A direct efficacy and safety comparison of insulin aspart, human soluble insulin, and human premix insulin (70/30) in patients with type 2 diabetes. Diabetes Care. 2004;27(5):1023-1027.
6. Dailey G, Rosenstock J, Moses RG, Ways K. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. Diabetes Care. 2004;27(10):2363-2368.
7. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. In: Siebenhofer A, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006:CD003287. doi:10.1002/14651858.CD003287.pub4.
8. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. Can Med Assoc J. 2009;180(4):385-397. doi:10.1503/cmaj.081041.
9. Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis. Diabetes, Obes Metab. 2009;11(1):53-59. doi:10.1111/j.1463-1326.2008.00934.x.
10. Rys P, Pankiewicz O, Łach K, Kwaskowski A, Skrzekowska-Baran I, Malecki MT. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: A systematic review. Diabetes Metab. 2011;37(3):190-200. doi:10.1016/j.diabet.2010.12.003.
11. Heller S, Bode B, Kozlovski P, Svendsen AL. Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. J Diabetes. 2013;5(4):482-491. doi:10.1111/1753-0407.12060.
12. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. In: Horvath K, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2007:CD005613. doi:10.1002/14651858.CD005613.pub3.
13. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes. Diabetes Res Clin Pract. 2008;81(2):184-189. doi:10.1016/j.diabres.2008.04.007.
14. DeVries JH, Gough SCL, Kiljanski J, Heinemann L. Biosimilar insulins: a European perspective. Diabetes, Obes Metab. 2015;17(5):445-451. doi:10.1111/dom.12410.
15. Blevins TC, Dahl D, Rosenstock J, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. Diabetes, Obes Metab. 2015;17(8):726-733. doi:10.1111/dom.12496.
16. Rosenstock J, Hollander P, Bhargava A, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). Diabetes, Obes Metab. 2015;17(8):734-741. doi:10.1111/dom.12482.
17. Segal D, Tupy D, Distiller L. The Biosulin equivalence in standard therapy (BEST) study - a multicentre, open-label, non-randomised, interventional, observational study in subjects using Biosulin 30/70 for the treatment of insulin-dependent type 1 and type 2 diabetes mellitus. S Afr Med J. 2013;103(7):458-460.
18. Turner R. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-853. doi:10.1016/S0140-6736(98)07019-6.
19. Investigators TOT. Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia. N Engl J Med. 2012;367(4):319-328. doi:10.1056/NEJMoa1203858.
20. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. N Engl J Med. 2008;359(15):1577-1589. doi:10.1056/NEJMoa0806470.
21. Turner R. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352(9131):854-865. doi:10.1016/S0140-6736(98)07037-8.
22. Erpeldinger S, Rehman MB, Berkhout C, et al. Efficacy and safety of insulin in type 2 diabetes: meta-analysis of randomised controlled trials. BMC Endocr Disord. 2016;16(1):39. doi:10.1186/s12902-016-0120-z.
23. Currie CJ, Poole CD, Evans M, Peters JR, Morgan CL. Mortality and Other Important Diabetes-Related Outcomes With Insulin vs Other Antihyperglycemic

Therapies in Type 2 Diabetes. J Clin Endocrinol Metab. 2013;98(2):668-677. doi:10.1210/jc.2012-3042.

24. Roumie CL, Greevy RA, Grijalva CG, et al. Association Between Intensification of Metformin Treatment With Insulin vs Sulfonylureas and Cardiovascular Events and All-Cause Mortality Among Patients With Diabetes. JAMA. 2014;311(22):2288. doi:10.1001/jama.2014.4312.
25. Ou H-T, Chang K-C, Li C-Y, Wu J-S. Risks of cardiovascular diseases associated with dipeptidyl peptidase-4 inhibitors and other antidiabetic drugs in patients with type 2 diabetes: a nation-wide longitudinal study. Cardiovasc Diabetol. 2016;15(1):41. doi:10.1186/s12933-016-0350-4.
26. Nyström T, Bodegard J, Nathanson D, Thuresson M, Norhammar A, Eriksson JW. Second line initiation of insulin compared with DPP-4 inhibitors after metformin monotherapy is associated with increased risk of all-cause mortality, cardiovascular events, and severe hypoglycemia. Diabetes Res Clin Pract. 2017;123:199-208. doi:10.1016/j.diabres.2016.12.004.
27. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Rydén L. Prognostic implications of glucose-lowering treatment in patients with acute myocardial infarction and diabetes: experiences from an extended follow-up of the Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study. Diabetologia. 2011;54(6):1308-1317. doi:10.1007/s00125-011-2084-x.
28. Chaitman BR, Hardison RM, Adler D, et al. The Bypass Angioplasty Revascularization Investigation 2 Diabetes Randomized Trial of Different Treatment Strategies in Type 2 Diabetes Mellitus With Stable Ischemic Heart Disease: Impact of Treatment Strategy on Cardiac Mortality and Myocardial Infarction. Circulation. 2009;120(25):2529-2540. doi:10.1161/CIRCULATIONAHA.109.913111.
29. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes. JAMA. 2016;316(3):313. doi:10.1001/jama.2016.9400.
30. Liu S-C, Tu Y-K, Chien M-N, Chien K-L. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. Diabetes, Obes Metab. 2012;14(9):810-820. doi:10.1111/j.1463-1326.2012.01606.x.
31. McIntosh B, Cameron C, Singh SR, Yu C, Dolovich L, Houlden R. Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and a sulphonylurea: a systematic review and mixed-treatment comparison meta-analysis. Open Med. 2012;6(2):e62-74.
32. Holman RR, Farmer AJ, Davies MJ, et al. Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes. N Engl J Med. 2009;361(18):1736-1747. doi:10.1056/NEJMoa0905479.
33. Holman RR, Thorne KI, Farmer AJ, et al. Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. N Engl J Med. 2007;357(17):1716-1730. doi:10.1056/NEJMoa075392.

Appendix 10.2: Insulin Preparations in South Africa

Basal Insulins

Insulin Type	Medicine Proprietary Name	Active Ingredients	Dosage Form	SEP (R)
Basal Analogue Insulins	Basaglar	Insulin Glargine	3x5 ml Cartridge	R523.57
	Basaglar	Insulin Glargine	3x5 ml Pen	R598.36
	Optisulin	Insulin Glargine	INJ	R623.30
	Levemir	Insulin Detemir	3x5 ml Cartridge	R678.14
	Lantus	Insulin Glargine	3x5 ml Pen	R688.84
	Levemir	Insulin Detemir	3x5 ml Pen	R800.88
Basal Human Insulins	Biosulin L	Lente Human Insulin	3x5 ml Cartridge	R346.24
	Biosulin N	Isophane Human Insulins	3x5 ml Cartridge	R346.24
	Humulin N		3x5 ml Cartridge	R450.54
	Humulin N		3x5 ml Pen	R450.55
	Protaphane HM		3x5 ml Pen	R627.47

Premix Insulins

Insulin Type	Medicine Proprietary Name	Active Ingredients	Dosage Form	SEP (R)
Premix Analogue Insulins	Humalog Mix25	Insulin Lispro + Insulin Lispro Protamine	3x5 ml Cartridge	R466.17
	Humalog Mix50		3x5 ml Cartridge	R466.17
	Humalog Mix25		3x5 ml Pen	R553.14
	Humalog Mix50		3x5 ml Pen	R553.15
	Humalog Mix 25		3x5 ml Pen	R595.66
	NovoMix 30	Biphasic Insulin Aspart	3x5 ml Pen	R603.37
	NovoMix 30		3x5 ml Cartridge	R643.76
	Ryzodeg®	Insulin Degludec+Aspart	3x5 ml Pen	R978.64
Premix Human Insulins	Biosulin 30-70	Biosynthetic Human Insulin: 30% Regular Insulin 70% Isophane Insulin	3x5 ml Cartridge	R346.24
	Humulin 30/70		3x5 ml Pen	R450.54
	Humulin 30/70		3x5 ml Cartridge	R450.54
	Actraphane HM		3x5 ml Pen	R593.07
	Actraphane HM		3x5 ml Pen	R627.47

Short/Rapid Acting Insulins

Insulin Type	Medicine Proprietary Name	Active Ingredients	Dosage Form	SEP (R)
Rapid Analogue Insulins	Humalog	Insulin Lispro	3x5 ml Pen	R432.82
	Humalog	Insulin Lispro	3x5 ml Cartridge	R432.82
	NovoRapid	Insulin Aspart	3x5 ml Cartridge	R487.62
	Apidra	Insulin Glulisine	3x5 ml Pen	R510.68
	NovoRapid	Insulin Aspart	3x5 ml Pen	R542.72
	Humalog	Insulin Lispro	3x5 ml Pen	R596.70
Short-Acting Human Insulins	Biosulin R	Regular Human Insulin (rDNA)	3x5 ml Cartridge	R346.24
	Humulin R		3x5 ml Pen	R370.59
	Humulin R		3x5 ml Cartridge	R430.83
	Actrapid HM (ge)		3x5 ml Pen	R491.94

Reference

South African Medicine Price Registery. Database Of Medicine Prices 14th March 2017. http://www.mpr.gov.za/Publish/ViewDocument.aspx?DocumentPublicationId=3285. [Accessed March 20, 2017.]

Appendix 10.3: Summary of meta-analyses and systematic reviews comparing rapid-acting insulin analogues to short-acting regular human insulin

Reference	Studies	Results
Siebenhofer *et al* 2006[1]	Studies published up to September 2005 Lispro (6 trials) Aspart (1 trial) No glulisine studies	HbA_{1c}: no significant difference Hypoglycaemia: no significant difference.
Singh *et al* 2009[2]	Studies published up to 2007 Included premix formulations Lispro (11 trials) Aspart (4 trials) No glulisine studies	HbA_{1c}: no significant difference Risk of hypoglycaemia: no significant difference.
Mannucci *et al* 2009[3]	Studies published up to January 2008 Lispro (7 trials) Aspart (4 trials) Glulisine (2 trials) Included premix formulations	HbA_{1c}: -0.10% in favour of analogues [95% CI, -0.01 to -0.19]. In 3 studies, blood glucose was significantly lower with analogues after breakfast (by 0.7 mmol/L) and dinner (by 0.6 mmol/L) (both $P < 0.001$). Severe hypoglycaemia: no significant difference.
Rys *et al* 2011[4]	Studies published up to July 2009 Included premix formulations Only studies on aspart (6 trials) or BIAsp (4 trials)	HbA_{1c}: no significant difference PPG: daily mean PPG lower by 1.18 mmol/L [95% CI,-1.88 to -0.47] with Aspart* Risk of hypoglycemia: no significant difference.
Heller *et al* 2013[5]	Patient-level data from trials comparing aspart with human insulin. Trials in type 1 diabetes (6 trials, n . 1909), type 2 diabetes (3 trials, n . 219), and types 1 and 2 diabetes combined (1 trial, n . 110)	HbA_{1c}: -0.10% in favour of Aspart [95% CI, -0.15 to -0.04], $p<0.001$ PPG: significantly lower by 0.47 mmol/L [95% CI, -0.70 to -0.25]; ($p<0.001$) with Aspart. Hypoglycaemia: no significant difference Nocturnal hypoglycaemia: significantly lower with Aspart: RR, 0.76 [95% CI, 0.67-0.85]; ($p < 0.001$).

BIAsp = biphasic insulin aspart; CI = confidence interval; HbA1c = glycated haemoglobin; PPG = postprandial glucose.
*Including studies of aspart and BIAsp

References:

1. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. In: Siebenhofer A, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006:CD003287. doi:10.1002/14651858.CD003287.pub4.
2. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. Can Med Assoc J. 2009;180(4):385-397. doi:10.1503/cmaj.081041.
3. Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis. Diabetes, Obes Metab. 2009;11(1):53-59. doi:10.1111/j.1463-1326.2008.00934.x.
4. Rys P, Pankiewicz O, Łach K, Kwaskowski A, Skrzekowska-Baran I, Malecki MT. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: A systematic review. Diabetes Metab. 2011;37(3):190-200. doi:10.1016/j.diabet.2010.12.003.
5. Heller S, Bode B, Kozlovski P, Svendsen AL. Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. J Diabetes. 2013;5(4):482-491. doi:10.1111/1753-0407.12060.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Appendix 13a: The management of hyperglycaemic emergencies

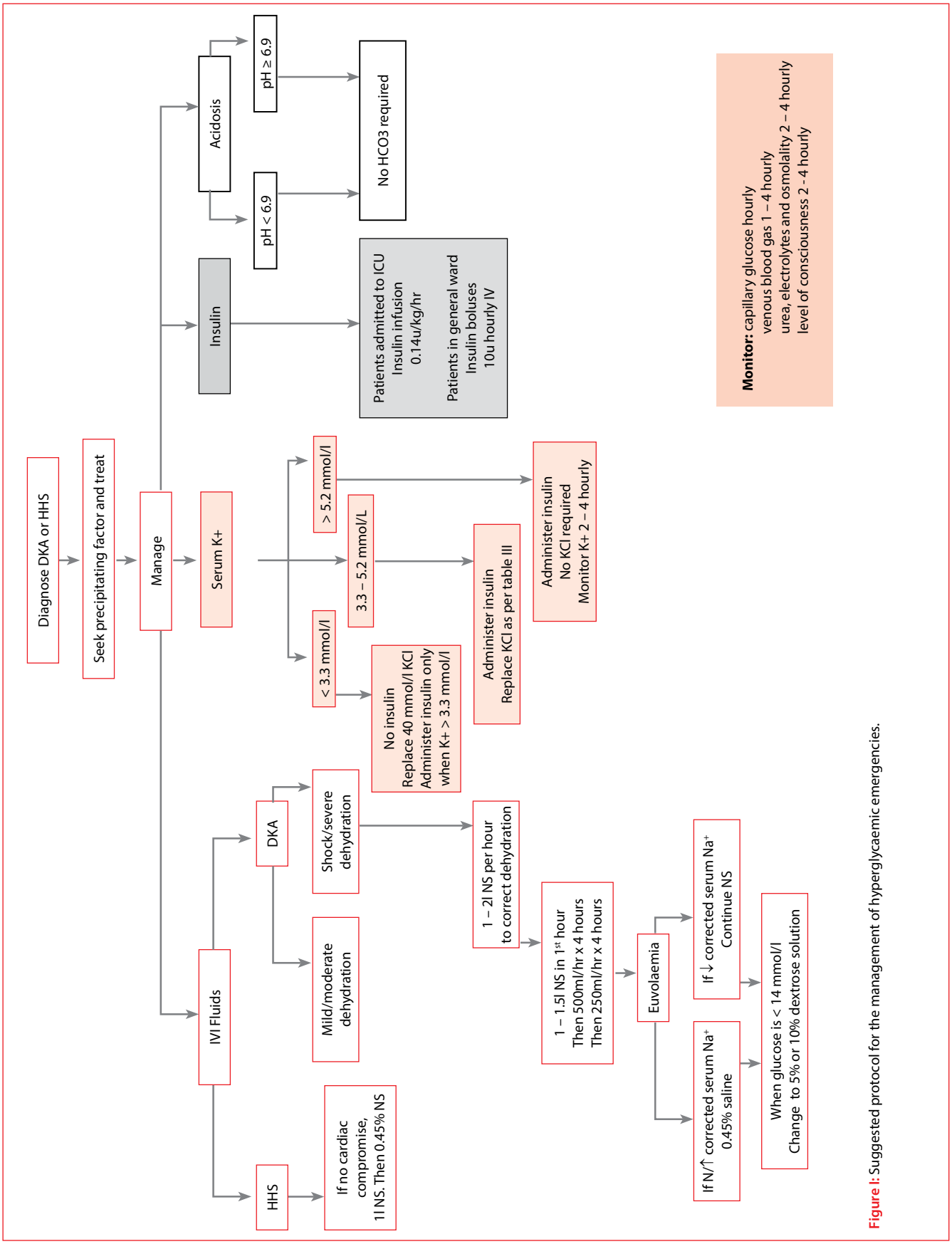


Figure I: Suggested protocol for the management of hyperglycaemic emergencies.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 13b:Diabetic Coma Chart

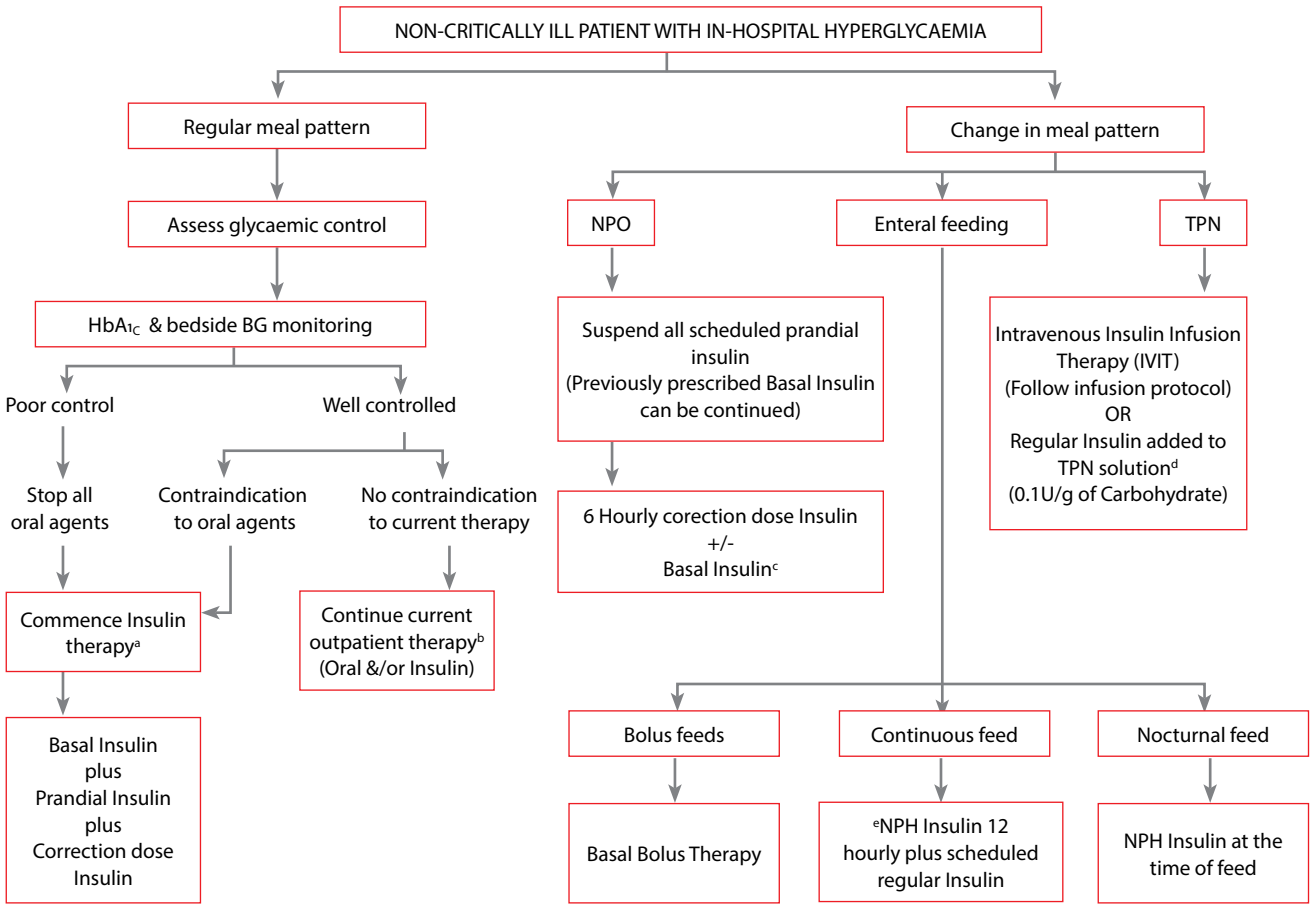
SEMDSA Type 2 Diabetes Guideline Expert Committee

Clinical Assessment						Urine		Blood Analysis													Treatment			
Time	Level. con.	Hydra-tion	BP	T^{O}	CVP	Ket-ones	Glu-cose	Glu-cose	Ket-ones	U	Cr	Na^{+}	K^{+}	Cl^{+}	PH	PCO_2	PO_2	Std Bic	Base xs	Osm	Fluids	Insulin	K^{+}	HCO_3

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Appendix 14: In-hospital management of diabetes algorithm



Algorithm: Approach to managing in-hospital hyperglycaemia in the non-critically ill patient
a: Total daily insulin dose ~ 0.2-0.5 IU/kg body weight
Basal bolus regimen or Split premix insulin (50% as basal insulin and 50% divided between meals as short or rapid acting insulin)
b: Consider dose reduction if decline in caloric intake anticipated
c: Once- or twice-daily NPH insulin or once-daily long-acting analogues
d: Alternative : Add 50% of Total Dose as Regular insulin to TPN AND 50% given as Basal insulin subcutaneously
e: Alternative : Premixed insulin 8 hourly or Long Acting Insulin Analogue given daily

BG: bedside glucose; NPO: nil per os, NGT: nasogastric tube; TPN: total parenteral nutrition

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Appendix 21.1: Diabetes footcare patient checklist

SEMDSA Type 2 Diabetes Guideline Expert Committee

Things you must DO…	Things you must NOT DO…
Wash the feet daily, using lukewarm water and soft soap.	Never soak your feet in standing water; always use running water. Do not use foot spa's.
Test the temperature of bath water with your hands before getting in. If you are unable to do so, let someone else test it.	Do not use heating appliances (heaters, electric blankets, hot water bottles) near your legs or feet.
Inspect (or ask someone else to inspect) the feet daily for cuts, cracks, bruises, blisters, corns calluses and damaged nails. Also check the areas between the toes for moistness, cracks and infection.	Do not cut corns or calluses yourself, or use corn plasters, chemicals or other remedies. These preparations are acidic and often cause ulcers. Consult a healthcare professional, because corns and calluses are an indication that there is a problem.
Wear clean cotton or wool socks or stockings that are dry and changed daily. Wear socks with the seams on the outside	Do not wear clothes or socks which restrict the blood flow to your feet. Never wear garters or socks with tight elastic tops.
Cut the toenails straight across and not too short . If the toenails cannot be cut, file them in a downward direction.	Do not cut down or around the corners of the toenails, as this may cause ingrown toenails (see Appendix 2)
If your vision is impaired, or your mobility is limited, ask someone to cut your toenails for you.	Do not use scissors or blades to cut your toenails.
Use moisturising creams (neutral water-based creams) for dry skin, but not between the toes. Use a powder for sweaty or moist skin.	Do not attempt to cut abnormally thickened toenails. Use a file instead or consult a healthcare professional.
Inspect the shoes and feel inside them for hidden objects before putting them on.	Do not use sharp instruments to dig around the toenails.
Dry the feet gently, especially between the toes. If using a blow-dryer to dry between the toes, ensure that it is set to blow cold air.	Do not smoke as this limits your blood circulation.
Report every injury, blister, cut, scratch or sore that develops to a healthcare professional.	Do not walk barefoot when indoors or outdoors. Many foot injuries occur inside the home.
Insist on having the feet professionally examined at least once a year by a health care professional.	

Footwear checklist	
Wear good shoes that fit well, and check that the shoes: • Are the correct length and width. • Allow enough room for the toes. • Have a smooth lining without seams. • Have a flexible sole that can bend easily. • Have a heel no higher than 4 cm	Buy footwear in the late afternoon, when the foot will be at its largest (because of swelling).
	New shoes should be comfortable; there should be no need to "break them in".
	Shoes should suit the activity to be undertaken.
	It is bad for your feet and posture to wear slippers all day. Slip-on shoes and slippers are not recommended.
Use a foot template to help with the selection of footwear.	Air your shoes every day, at night while you sleep or during the day when you rest.
Shoes should follow the natural outline of the foot, and fit the widest part of the foot.	Do not wear worn-out shoes, socks or stockings.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 21.2: Diabetes foot screening assessment form

SEMDSA Type 2 Diabetes Guideline Expert Committee

Screening to Detect the High Risk Diabetic Foot

Name:		If all responses are circled "No", rescreen in 1 year	If ANY response is circled "YES" categorise the risk (see Appendix)
Phone#: Age			
Diabetes Duration: Gender: M F			
Date of Exam:			
HISTORY			
1	Previous ulcer	No	Yes
2	Previous amputation	No	Yes
SKIN			
3	Active ulcer	No	Yes
4	Ingrown toenail	No	Yes
5	Calluses (thickened plantar skin)	No	Yes
6	Blisters	No	Yes
7	Fissures (linear cracks)	No	Yes
	Remember to check the 4th and 5th web spaces and nails for fungal infection		
BONES			
8	Deformity (hammer toes, bunion, arch, Charcot foot)	No	Yes
9	Fixed joint (no movement) at ankle and/or big toe	No	Yes
NERVES			
10	**Monofilament Big Toes**	No neuropathy if ≥ 7 of 8 felt	Yes Possible neuropathy if ≤ 6 of 8 felt
	Right big toe /4 felt		
	Left big toe /4 felt		
11	**Ipswitch Touch The Toes Test**	No neuropathy if ≥ 5 of 6 felt	Yes Possible neuropathy if ≤ 4 of 6 felt
	Right foot /3 felt		
	Left foot /3 felt		
Vasculature			
	Absent dorsalis pedis or posterior tibial pulse	No	Yes

Adapted from Wound Healing Association of South Africa guideline[1]
1. Available from http://www.woundhealingsa.co.za/index.php/WHSA/article/view/185, (cited on 24 February 2016)

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 21.3: Foot abnormalities and footwear illustrations

SEMDSA Type 2 Diabetes Guideline Expert Committee

Fig 1: How to clip toenails

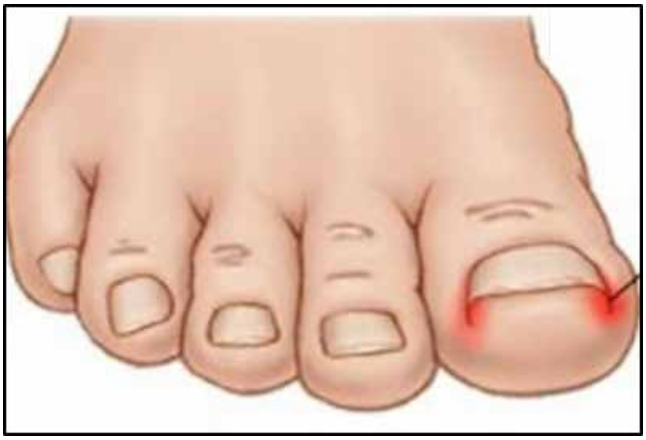


Fig 2: Ingrown toenail

Fig 3: Dystrophic nails due to fungal nail infection. Onychodystrophy can also be caused by trauma to the nailbed.

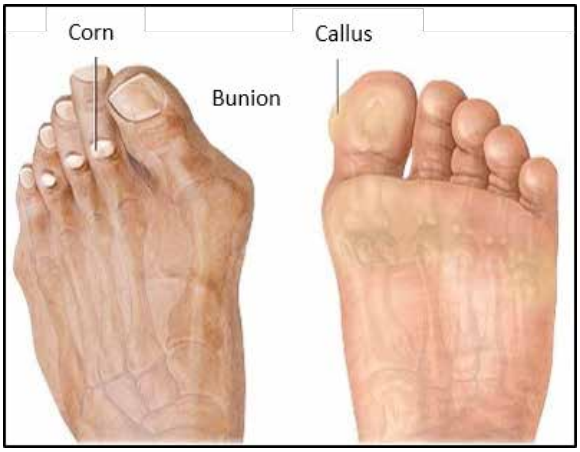


Fig 4: Corns, callus and bunion (hallux valgus)

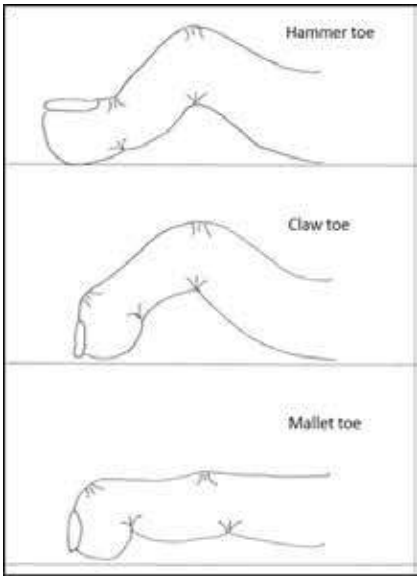


Fig 5: Types of hammer toe deformities

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Appendix 21.3: Foot abnormalities and footwear illustrations (continued)

SEMDSA Type 2 Diabetes Guideline Expert Committee

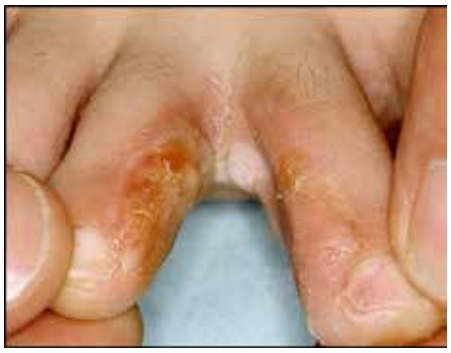


Fig 7: Tinea pedis

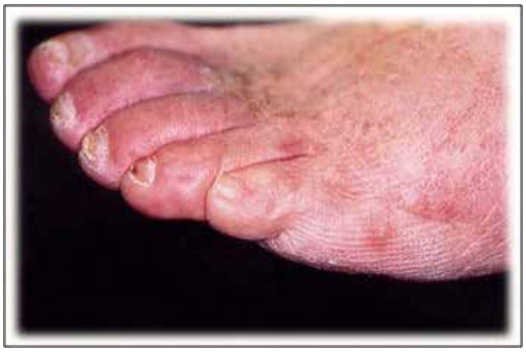


Fig 8: Red marks are a sign of ill-fitting footwear

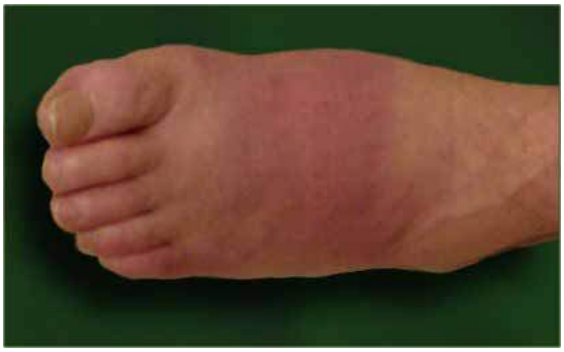


Fig 9: Acute Charcot foot is swollen red and warm to the touch

Fig 10: Good shoes follow the shape of the foot

Fig 10: Good shoes are built for comfort

Fig 11: The foot template aids in choosing the correct width and length for shoes.

Fig 6: Foot arch deformities: pes cavus (high arch) and pes planus (flat foot)

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Appendix 21.4: Neuropathy assessment

These methods are designed to screen for the presence or absence of diabetic neuropathy, as opposed to screening for specific sites on the feet that are at risk of ulceration (multisite testing). If neuropathy is identified by either of these methods, other sites may be tested to identify high-risk areas for ulceration.

Rapid Screening for Diabetic Neuropathy Using the 10g Semmes-Weinstein Monofilament

1. Show the 10-g Semmes-Weinstein monofilament to the patient.
2. Touch it first to the patient's forehead or sternum so that the sensation is understood.
3. Instruct the patient to say "yes" every time the monofilament stimulus is perceived.
4. With the patient's eyes closed, apply the monofilament to the dorsum of the great toe proximal to the nail bed as shown in the illustration below. Use a smooth motion – touch the skin, bend the filament for a full second, then lift from the skin.
5. Perform this stimulus 4 times per foot in an arrhythmic manner so the patient does not anticipate when the stimulus is to be applied.
6. Add up all correct stimuli for a score out of 8. A score of 7 or 8 correct responses likely rules out the presence of neuropathy.

Rapid Screening for Diabetic Neuropathy Using the 128Hz Tuning Fork (The "On-Off" Method)

1. Strike the tuning fork against the palm of your hand hard enough that it will vibrate for approximately 40 seconds.
2. Apply the base of the tuning fork to the patient's forehead or sternum and ensure that the vibration sensation (not just the touch sensation) is understood.
3. With the patient's eyes closed, apply the tuning fork to the bony prominence situated at the dorsum of the first toe just proximal to the nail bed. Ask if the vibration sensation is perceived.
4. Ask the patient to tell you when the vibration stimulus is stopped, and then dampen the tuning fork with your other hand.
5. One point is assigned for each vibration sensation perceived (vibration "on"). Another point is assigned if the correct timing of dampening of the vibration is perceived (vibration "off ").
6. Repeat this procedure again on the same foot, then twice on the other foot in an arrhythmic manner so the patient does not anticipate when the stimulus is to be applied.
7. Add up all correct stimuli for a score out of 8. A score of 7 or 8 correct responses likely rules out the presence of neuropathy.

Reproduced with permission from the Canadian Diabetes Association Clinical Practice Guidelines (2008).[1]
Monofilaments can be ordered from
Noy Pullen: email: linoia@mweb.co.za; Tel: 0722587132
Medis, Cape Town: e-mail info@medismedical.com; Tel: 021-9828211

Appendix 21.4: Neuropathy assessment (continued)

Rapid Screening for Diabetic Neuropathy Using the Ipswitch Touch the Toes Test

1. Remove socks and shoes and rest the subject with their feet lying on a sofa or bed.
2. Remind them which is their RIGHT and LEFT leg, pointing this out by firmly touching each leg, saying *"this is your right"* when the right leg is touched and *"this is your left side"* when the left is touched. If you face the soles of their feet their right is on your left.
3. Ask them to close their eyes and keep them closed until the end of the test.
4. Inform them that you are going to touch their toes and ask them to say right or left as soon as they feel the touch and depending on which foot was touched.
5. Perform the touch, using your index (pointing finger) as shown in the photo and diagrams.
6. The picture also shows which six toes should be touched and the sequence.
7. Start by lightly touching the tip of the toe marked 1 (right big toe) with the tip of your index finger. The patient will respond by saying *"right"* if they feel the touch.

Very Important

- The touch must be light as a feather, and brief (1–2 seconds): do not press, prod or poke, tap or stroke the skin.
- If the person did not respond do not attempt to get a reaction by pressing harder. They did not feel; this should be recorded as not felt.
- You must not touch each toe more than once.
- If not felt do not repeat the touch, there is no second chance.
- 2 or more spots absent qualifies as neuropathy

Adapted from Touch The Toes Test by Diabetes UK based on The Ipswich Touch Test: a simple and novel method to screen patients with diabetes at home for increased risk of foot ulceration. Sharma S, Kerry C, Atkins H, Rayman G. Diabet Med. 2014 Sep;31(9):1100-3.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

Appendix 21.5: Care Pathway for People with Diabetic Foot Problems[1]

At diagnosis and annually thereafter a trained healthcare worker (nurse, doctor, community health worker) must examine patient's feet without socks or bandages to determine risk status:

- Inspect for foot deformities, and skin and nail abnormalities
- Inspect footwear
- Test sensation (monofilament, 128 Hz tuning fork or "touch the toe")
- Palpate dorsalis pedis and posterior tibial pulses

Training of HCW should be done by diabetes specialists, podiatrists or specialist nurses

Clinical Findings:	**Clinical Findings:**	**Clinical Findings:**	**Clinical Findings:**
• No previous ulcer or amputation • No deformities • Normal sensation • No PAD	Any one of: • Foot deformity • Loss of sensation • PAD	Previous ulcer or amputation, or 2 or more of: • Foot deformity • Loss of sensation • PAD • Visually impaired • On renal replacement	Any of: • Active foot ulcer • Gangrene • Spreading infection • Critical limb ischaemia • Charcot foot
Low Risk	**Moderate Risk**	**High Risk**	**Active Foot Disease**
Management • Structured footcare education • Annual foot screen in primary care	Management • Ongoing education in foot protection • Foot examination at every clinic visit • Vascular, podiatry, orthotics, diabetes specialist referral as needed	Management • Ongoing education in foot protection • Foot examination at every visit • Multi-disciplinary referral within 1 month, co-ordinated by senior diabetes consultant	Management • Ongoing education in foot protection • Foot examination at every visit • Multi-disciplinary referral within 24 hours, co-ordinated by senior diabetes consultant

Management for all patients

- Structured patient education
- Control of glycaemia, blood pressure, dyslipidaemia and obesity

PAD: Peripheral arterial disease i.e. both pulses absent in at least one foot, or other signs and symptoms (claudication, pallor, dependent rubor, reduced venous filling, poor skin and tissue vitality)

1. Adapted from National Diabetes Programme, Clinical Strategy and Programmes Directorate. Model of Care for the Diabetic Foot (Ireland). 2014 available at http://www.hse.ie/eng/about/Who/clinical/natclinprog/diabetesprogramme/modelofcarediabetes.pdf (Accessed 21 December 2016)

Appendix 26: Ramadan dietary recommendations and meal plans

Caloric distribution	1200 kcal/day			
Macronutrient Composition	**CHO: 45–50%:** Recommended: low GI, low GL, whole grain and high fibre. **Protein: 20–30%:** Recommended: fish, skinless poultry, non-fat or dairy, nuts, seeds and legumes. **Fat: < 35%:** Recommended: SFA <10%, choose low-fat cooking methods e.g. grill, bake and steam			
Recommended for	Weight reduction for women <150 cm tall	Weight maintenance for women <150 cm tall & weight reduction for women >150 cm tall	Weight maintenance for women >150 cm tall & weight reduction for men	Weight maintenance for women >150 cm tall & for men
Lifestyle reccomendations	Begin iftaar with plenty of water to overcome dehydration from fasting; Keep physically active; Do not sleep for longer than usual			
Suhur (Morning) 30–40% of total calories	**300–480 kcal** • Whole grain bread- 1 slice, with egg- 1 large • Low-fat milk- 4 tbsp, with oats- 3 tbsp and almonds- ½ handful • Apple- 1 • Water/unsweetened drinks (365 kcal, CHO exchange = 3)†	**450–600 kcal** • Whole grain bread- 2 slices, with egg- 1 large • Low-fat milk- 4 tbsp, with oats- 3 tbsp and almonds- ½ handful • Apple- 1 • Water/unsweetened drinks (475 kcal, CHO exchange = 4)	**540–720 kcal** • Whole grain bread- 2 slices, with egg- 1 large • Low-fat milk- 4 tbsp, with oats- 6 tbsp and almonds- 1 handful • Low fat yogurt- 0.5 tub • Apple- 1 small • Water/unsweetened drinks (555 kcal, CHO exchange = 4.5)†	**600–800 kcal** • Whole grain bread- 2 slices, with egg- 1 large • Low-fat milk- 4 tbsp, with oats- 6 tbsp and almonds- 1 handful • Low fat yogurt- 0.5 tub • Apple- 1 small • Water/unsweetened drinks (640 kcal, CHO exchange = 5.5)
Snack 1 10–20% of total calories	**120–240 kcal** • Dates: 1–2 • Badam milk (low-fat milk, ground almonds- ½ handful and cardamom powder)- 1 glass (210 kcal, CHO exchange = 2)	**150–300 kcal** • Dates: 1–2 • Badam milk (low-fat milk, ground almonds- ½ handful and cardamom powder)- 1 glass (210 kcal, CHO exchange = 2)	**180–360 kcal** • Dates- 1–2 • Badam milk (low-fat milk, ground almonds- ½ handful and cardamom powder)- 1 glass (210 kcal, CHO exchange = 2)	**200–400 kcal** • Dates- 1–2 • Badam milk (low-fat milk, ground almonds- ½ handful and cardamom powder)- 1 glass (210 kcal, CHO exchange = 2)
Iftaar (Evening) 40–50% of total calories	**480–600 kcal** • Baked mince samosas- 2–3 • Haleem (wheat, oats and meat broth)- ½ cup • Basmati/parboiled rice- 0.5 cup/ roti- 1 small • Grilled or curried lean chicken/ fish- 4 oz • Salad/vegetables • Water/unsweetened drinks (490 kcal, CHO exchange = 3)	**600–750 kcal** • Baked mince samosas- 2–3 • Haleem (wheat, oats and meat broth)- 1 cup • Basmati/parboiled rice- 0.5 cup/ roti- 1 small • Grilled or curried lean chicken/ fish- 4 oz • Salad/vegetables • Water/unsweetened drinks (635 kcal, CHO exchange = 4)	**720–900 kcal** • Baked mince samosas- 2–3 • Haleem (wheat, oats and meat broth)- 1 cup • Basmati/parboiled rice- 1 cup/ roti- 2 small • Grilled or curried lean chicken/ fish- 4 oz • Salad/vegetables • Water/unsweetened drinks (710 kcal, CHO exchange = 5)	**800–1000 kcal** • Baked mince samosas- 2–3 • Haleem (wheat, oats and meat broth)- 1.5 cups • Basmati/parboiled rice- 1 cup/ roti- 2 small • Grilled or curried lean chicken/ fish- 4 oz • Salad/vegetables • Fruit, 1 piece • Water/unsweetened drinks (850 kcal, CHO exchange = 6)
Snack 2 10–20% of total calories	**120–240 kcal** • Unsweetened fruit in their juice- ½ cup • Water/unsweetened drinks (120 kcal, CHO exchange = 1)	**150–300 kcal** • Milk-based dessert with sweetener (phirni/falooda/rasmalai)- 1 cup • Water/unsweetened drinks OR • Unsweetened fruit in their juice- 1 cup, with custard and sweetener- 0.5 cup (235 kcal, CHO exchange = 2.5)	**180–360 kcal** • Milk-based dessert with sweetener (phirni/falooda/rasmalai)- 1 cup • Water/unsweetened drinks OR • Unsweetened fruit in their juice- 1 cup, with custard and sweetener- 0.5 cup (235 kcal, CHO exchange = 2.5)	**200–400 kcal** • Milk-based dessert with sweetener (phirni/falooda/rasmalai)- 1 cup • Water/unsweetened drinks OR • Unsweetened fruit in their juice- 1 cup, with custard and sweetener- 0.5 cup (235 kcal, CHO exchange = 2.5

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

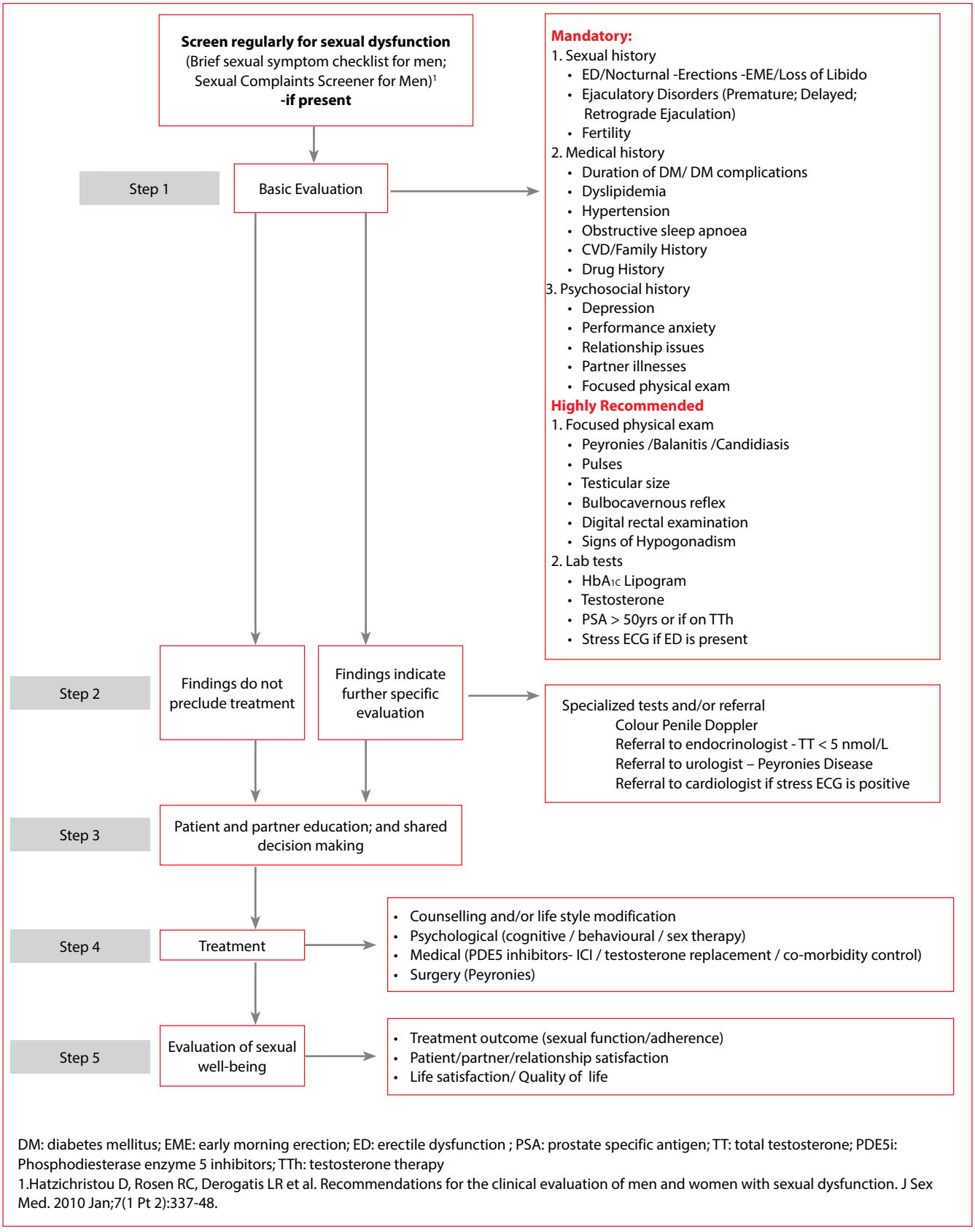
Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1)
http://dx.doi.org/10.1080/16089677.2015.1056468

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

SEMDSA GUIDELINES

Appendix 29: The evaluation of male sexual dysfunction in type 2 diabetes

SEMDSA Type 2 Diabetes Guideline Expert Committee



DM: diabetes mellitus; EME: early morning erection; ED: erectile dysfunction ; PSA: prostate specific antigen; TT: total testosterone; PDE5i: Phosphodiesterase enzyme 5 inhibitors; TTh: testosterone therapy

1.Hatzichristou D, Rosen RC, Derogatis LR et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med. 2010 Jan;7(1 Pt 2):337-48.