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The 2012 SEMDSA Guideline for the Management of Type 2 Diabetes (Revised)

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SEMDSA
Society for Endocrinology, Metabolism and Diabetes of South Africa

Special Guideline Edition

The 2012 SEMDSA Guideline for the Management of Type 2 Diabetes

Much has been written recently about the burden of noncommunicable diseases (NCDs),[1] and the recent United Nations High Level Summit on Non-Communicable Diseases in September 2011 served to highlight a call to action globally. One hundred and ninety-three Member States, with 34 Heads of State (including our own President), adopted the historic Political Declaration on Non-Communicable Disease Prevention and Control. This is the first ever Political Declaration on NCD, and includes 22 commitments to which governments worldwide must now be held accountable. Importantly for people with diabetes mellitus (diabetes), the Declaration commits governments to increasing access to affordable, safe, effective and quality-assured medicines and technologies. Diagnostics are equally as important as medicines for people with diabetes. Crucially, the Declaration commits governments to improve diagnostic services, including by increasing capacity of laboratory services, and collaboration with the private sector to improve affordability, accessibility and maintenance of diagnostic equipment and technologies. The central role that people with diabetes and NCDs play is made clear in the Declaration. It commits governments to a nationally driven and comprehensive response to NCDs, with the full and active participation of people living with the diseases. It also acknowledges the importance of health literacy and patient empowerment in care, and the role of patient organisations in the provision of NCD services.

The International Diabetes Federation (IDF) estimated that, in 2011, 366 million people worldwide were living with diabetes, and that 80% of these individuals live in low- and middle-income countries.[2] It is projected that, by 2030, the number would have risen to 552 million. According to the IDF, the estimated diabetes prevalence for South Africa is 6.46% for adults aged 20-79 years (approximately 1.9 million of 30 million adults). The self-reported rate of known diabetes (type 1 and 2) in the South African Second Demographic and Health Survey of 2003 was unchanged from 1998 (6.5% of persons older than 15 years).[3] However, it must be noted that 50-85% of diabetes sufferers (especially in rural areas) remain undiagnosed. The high prevalence of diabetes (and other NCDs) is closely linked to rapid cultural and social changes, ageing populations, increasing urbanisation, unhealthy eating and reduced physical activity. How are we to stem the tide?

Type 2 diabetes is not a particularly well-managed disease, with fewer than 50% of patients meeting glycaemic targets, even in developed countries. More disturbingly, fewer than 10% achieve glycaemic, lipid and blood pressure targets, despite evidence that multifactorial interventions are extremely effective at improving morbidity and mortality outcomes.[4] Limited local data suggest that more than two thirds of type 2 diabetes patients in South Africa have a glycated haemoglobin (HbA_{1c}) level above the generally recommended target of 7%.[5]

The need for a guideline to manage the high burden of disease that is type 2 diabetes is therefore quite obvious. It provides a framework for training healthcare professionals, helps guide rational management decisions and limits wastage of scarce resources on treatments and technologies that are outdated or dangerous. Importantly, a guideline also assists the funders of health care to plan ahead and formulate strategies for the future. Government departments and health insurers need to take cognisance of the standards of care that need to be provided for the citizens of our country, and need to be held accountable for failures when these occur. A national guideline removes ignorance as a defense against lack of service delivery.

The last SEMDSA type 2 diabetes Guideline was revised in 2008 and published in this journal in 2009.[6] That Guideline was entitled "SEMDSA Guidelines for Diagnosis and Management of Type 2 Diabetes Mellitus for Primary Health Care – 2009", with the emphasis on "primary health care". Unfortunately, it was misconstrued, particularly by the funders of health care (both public and private), and applied as a definitive guideline at all levels of care. We hope that this does not recur. It is also noteworthy that interventions mentioned in that Guideline are still not accessible to the majority of our patients in South Africa. Referrals to dietitians and diabetes educators and measurement of HbA_{1c}, serum creatinine and microalbumin are simply not available or accessible for many, if not most, of our patients.

Since the publication of the 2009 Guideline, there have been many new developments that needed updating in the current Guideline. HbA_{1c} has now been validated as a diagnostic tool and accessibility to internationally standardised assays is improving, new data have emerged with regard to glucose, blood pressure and cholesterol

target levels, and the risks of hypoglycaemia for cardiovascular events and death are being recognised. Additionally, the dangers of older therapeutic agents (glibenclamide and thiazolidenediones) have come to light, and the potential benefits of other agents (incretins and alpha-glucosidase inhibitors) for avoiding weight gain and hypoglycaemia are now being appreciated. These and other developments have necessitated the rewriting of large sections of the 2009 Guideline.

The purpose of the Guideline is to improve healthcare delivery, and ultimately to translate into improvements in quality and quantity of life for our patients. To achieve this goal a number of simultaneous initiatives will be necessary:

- The Guideline must be accepted by all stakeholders (healthcare professionals, regulators of health care and patients) as a minimum standard of care for type 2 diabetes.
- Regulators and funders of health care must ensure that facilities and resources are made available for the practical implementation of these guidelines.
- Non-governmental organisations (NGOs) and lobby groups must take up the challenge of holding regulators and funders of health care accountable for failure to implement the care processes outlined in the Guideline. The newly formed alliance in the United Diabetes Association [SEMDSA, Diabetes South Africa (DSA) and the Diabetes Educators Society of South Africa (DESSA)] will play a pivotal role here.
- The Guideline must be disseminated widely and systems must be in place to ensure that even practitioners in the most remote parts of our country have access to it and understand how to use it in daily practice. A short summary version of the guideline will be published soon to improve its practical day-to-day usage. Structured CME programmes, coordinated by SEMDSA and the Association of Clinical Endocrinologists, should be used to oversee this process.
- A method for measuring the impact of the Guideline on healthcare delivery and outcomes needs to be established. This should be the responsibility of SEMDSA, the Department of Health and the funders of health care.

Finally, some introspection on the part of SEMDSA is appropriate. There is no doubt that SEMDSA (including academic training units and the Association of Clinical Endocrinologists) is and ought to be caretaker for diabetes in South Africa. Yet we are all confronted, on a daily basis, with patients where we can speak not of the standard of care but the standard of neglect; patients whose first serum creatinine is measured at the time of end-stage renal failure, patients needing amputations who have never had their feet examined, or patients with deplorable glycaemic control where no therapeutic adjustments have been made for years. I believe that change will come from empowering our patients. Through education and publicity we must empower them to demand the services and levels of care that are set out in this guideline, and to hold us all (funders, government, doctors, nurses etc.) accountable when the system fails them. Someone needs to answer to every case of amputation, blindness and renal failure. If we sit back and continue to accept the diabetes disasters that confront us daily, without informing our patients of the failures in the system, then we are guilty of colluding with the system and reneging on our Hippocratic Oath. The words that brought change to our country will also bring change to diabetes.

Amandla! Power to the people!

Aslam Amod
Chairperson: SEMDSA and the Association of Clinical Endocrinologists of South Africa

Acknowledgement

I wish to acknowledge all those involved in the development of the Guideline. It was a mammoth task and required immense commitment from everyone. I particularly wish to thank the Steering Committee for their hard work, Shelley Harris for her administrative assistance, and Douw Greeff from Medpharm Publications for his patience.

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Foreword

Disclaimer

This guideline is not intended to replace professional judgement, 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 care level.

The Guideline development process

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

1. The broad topic of type 2 diabetes management was divided into smaller sections. The SEMDSA executive committee then invited experts with a special interest in the relevant section to lead the guideline development for that section. This *Steering Committee* were at liberty to enlist the assistance of other experts to develop the sectional guideline.
2. The Steering Committee was tasked with reviewing the updated literature and the Department of Health's draft type 2 diabetes guideline document relevant to the allocated section, and to generate an updated set of recommendations (based on best evidence and best practice) for their allocated section.
3. A Guideline Meeting was held in Johannesburg on 23 September 2011. The following participants were invited to this meeting *(The Advisory Committee)*:
   a. SEMDSA Excom
   b. The Steering Committee
   c. All members of the Association of Clinical Endocrinologists of South Africa (ACE-SA, a subgroup of SEMDSA)
   d. Representatives from the Department of Health
   e. Representatives from the Council of Medical Schemes
   f. Representatives from Faculty of Consulting Physicians of South Africa, Society of General / Family Practitioners, Diabetes Educators Society of South Africa and Diabetes South Africa.
   g. Representatives from Medical Schemes

   The meeting was funded using unrestricted educational grants from all pharmaceutical companies involved in the field of diabetes and metabolic diseases. Two representatives from each company were allowed observer status at the meeting (i.e. they were not allowed to participate in the proceedings of the meeting).
4. At the Guideline Meeting, each member of the Steering Committee was required to present the proposed updated guideline for the allocated section to the audience. The information presented was interrogated and amendments and additions were suggested. The discussions were evidence based, but where evidence was lacking, a consensus among participants was adopted. The Committee was guided by 'best practice' and not economic analyses (the committee had no expertise in the area of the health economics, and accurate data regarding healthcare expenditure for diabetes is lacking in South Africa). However, this was difficult to achieve and some decisions did indeed take economic considerations into account.
5. Two ACE-SA members recorded detailed minutes of the discussions and debates at the meeting.
6. After the Guideline Meeting, these minutes were circulated to the Steering Committee. The Steering Committee had to amend / rewrite their sections as per recommendations from the Guideline Meeting. These revised draft documents were then posted on the SEMDSA secure website for further comments from SEMDSA members and the Department of Health.
7. After receiving final comments and the documents were revised where necessary and draft guideline for each section was submitted to Medpharm Publishers for copy-editing and to lend uniformity to writing style and layout. The Chairperson and a smaller subcommittee reviewed the copy-edited document.

It was hoped that the guideline would give clear guidance with regards to the levels of care i.e. the requirements at primary, secondary and tertiary healthcare levels. This was not achieved and will remain a challenge for future guideline development. In the meantime this guideline focuses on Primary Care where the majority of type 2 diabetes patients are managed.

Acknowledgements

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- Ms Shelley Harris (SEMDSA secretariat) for her efficient administrative and logistical assistance in co-ordinating the guideline process.
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- Dr. Helena Oosthuizen and Prof. Willie Mollentze for keeping detailed records of the Guideline Meeting.
- Douw Greeff and Medpharm Publications for professional assistance 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).

Website

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

The Guideline Committee

Chairperson
Aslam Amod

Sections	Steering Committee
Definition, classification, diagnosis and screening	Ayesha Motala
Organisation of Diabetes Care	Naomi Levitt
Diabetes self management education, Medical nutrition therapy	Jeannie Berg, Madelein Young, Natalie Grobler
Physical activity and type 2 diabetes	Andrew Heilbrunn
Assessment of Glycaemic Control	Larry Distiller
Glycaemic control: Non-insulin therapies, insulin-based therapies and the SEMDSA 2012 algorithm	Aslam Amod, Fraser Pirie, Joel Dave
Hypoglycaemia, Diabetes in pregnancy	Ken Huddle
Hyperglycaemic emergencies	Daksha Jivan
In-hospital management of type 2 diabetes	Imran Paruk
Obesity in type 2 diabetes	Wayne May
Cardiovascular risk and dyslipidaemia	Derick Raal, Dirk Blom
Aspirin therapy	Brynne Ascott-Evans
Hypertension	Susan Brown
Chronic kidney disease and Retinopathy	Willie Mollentze
Neuropathy and foot problems in type 2 diabetes	Paul Rheeder, Lynn Tudhope, Gerda Janse van Rensburg
Type 2 diabetes in children and adolescents, management of sick days	Yasmin Ganie, Michelle Carrihill
Type 2 diabetes in older persons	Sophie Rauff
Type 2 diabetes in high risk ethnic groups	Danie van Zyl
Type 2 diabetes during Ramadaan	Hoosen Randeree
Type 2 diabetes in HIV infected individuals	Duma Khutsoane
Prevention/Delay of Type 2 Diabetes	Pankaj Joshi
Diabetes and driving	Peter Raubenheimer

Advisory Committee

SEMDSA Executive Committee (Excom)	Aslam Amod (Chairperson), William Ferris (Vice-chairperson), Joel Dave (Treasurer), Michelle Carrihill, Daksha Jivan, Ayesha Motala, Willie Mollentze, Fraser Pirie,
Other SEMDSA members	Gregory Arthur Hough, Brian Kramer, Stanley Landau, Puvanesveri Naiker, Mahomed Omar, Helena Oosthuizen, William Toet, Carsten Weinreich, Holger Wellmann
Department of Health (Chronic Diseases)	Anne Croasdale, Melvyn Freeman, Sandhya Singh
Society of General / Family Practitioners,	Angelique Coetzee, Philip Erasmus
Diabetes Education Society of South Africa	Jeannie Berg, Gerda van Rensburgh, Madelein Young
Diabetes South Africa	Leigh-Ann Bailie , Ranga Kuni
Medical Aids	Margaret Campbell (Discovery)
Council of Medical Schemes	Selaelo Mametja

1. The 2012 SEMDSA Guideline for the Management of Type 2 Diabetes

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1. Introduction

Type 2 diabetes mellitus (diabetes) is a major public health problem, and accounts for more than 90% of all diabetes cases. The insidious and initially asymptomatic nature of the disease results in patients not seeking early medical attention, so that 30-85% of cases of type 2 diabetes remain undiagnosed. At the time of eventual diagnosis, approximately 20% of patients will already have complications of the disease.

In 2003, the International Diabetes Federation (IDF) estimated that there would be 285 million people with diabetes by 2010. This was a gross underestimate, as the fifth edition of the *IDF Atlas* shows that there were 366 million diabetes sufferers worldwide in 2011 (183 million of these were undiagnosed). The conservative South African estimate is that 6.5% of adults aged 20-79 years have diabetes, but age-adjusted prevalences of up to 13% have been described in urban populations as far back as 1994. The effects of urbanisation and an unhealthy lifestyle are important contributors to the rising prevalence of obesity and diabetes. The 2003 Demographic and Health Survey showed that 30% of South Africans are overweight or obese.

The link between urbanisation, sedentary lifestyles, unhealthy eating and rising levels of obesity and type 2 diabetes has been demonstrated universally, and effective prevention of obesity and type 2 diabetes requires a paradigm shift from a patient-centred approach to a "whole of government" and a "whole of society" approach. Hence, government departments (e.g. Health, Agriculture, Trade and Industry, Sport and Recreation, Education), together with nongovernmental organisations, need to join forces in preventing and combating diabetes. Collaborating partners must effectively work together at all levels of service delivery.

It is imperative that focused screening of high-risk persons be introduced to improve the rate of early detection, thereby reducing late entry with established long-term complications into the health system. Early good control of glycaemia, blood pressure and dyslipidaemia, together with regular examinations for microvascular and macrovascular complications with appropriate and timely interventions, is the only way to prevent or reduce morbidity and mortality.

Well-organised clinics, with adequate staff suitably trained in diabetes care that use effective protocols and appropriate tools, will facilitate improved quality of diabetes care. This Guideline aims to assist in achieving this objective. The guideline's target audience is mainly primary healthcare providers, though all healthcare professionals and funders (public and private sectors) should also derive benefit from it. However, this Guideline will only be effective if it is widely distributed and followed. The Department of Health, through its Non-Communicable Disease Directorate, has committed to utilising and implementing this Guideline. It is hoped that private health-sector funders also use this Guideline to establish minimum care standards for type 2 diabetes. Systems will need to be in place to measure appropriate Guideline usage and outcomes. If this should happen, SEMDSA would have achieved its objective of ensuring adequate care for *all* South Africans with type 2 diabetes.

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2. Definition and classification of diabetes mellitus

Since 1965, there have been several guidelines for the classification and diagnosis of diabetes mellitus. The first standardised guidelines were published almost 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.

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2.1 Definition of diabetes mellitus

Diabetes mellitus (diabetes) is a metabolic disorder with heterogenous 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.[1-3]

Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision and weight loss. 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 treatment sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made. With the rising global prevalence of diabetes, some of the greatest increases in prevalence have been seen in resource–limited developing nations. 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/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.[1,5]

2.2 Classification of diabetes and other categories of glucose tolerance[1-4]

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

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.

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. The 2011 World Health Organization (WHO) Consultation affirms the position taken by the 2006 WHO/IDF (International Diabetes Federation) consultation, that no further change should be made to the 1999 WHO recommendations on the diagnostic criteria for these states, discourages the use of the term "pre-diabetes" to describe IGT and IFG, and endorses the continued use of the collective term "intermediate hyperglycaemia".[5]

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.[1]

The *aetiological types* of diabetes are type 1, type 2, other specific types and gestational diabetes. Patients with any form of diabetes may require insulin

Table I: Aetiological classification of diabetes mellitus[3]

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 predominantly secretory defect with insulin resistance.

III. Other specific types
A. Genetic defects of β-cell function
Chromosome 12, HNF-1α (MODY3), chromosome 7, glucokinase (MODY2), chromosome 20, HNF-4α (MODY1), chromosome 13, insulin promoter factor-1 (IPF-1; MODY4, chromosome 17, HNF-1β (MODY5), chromosome 2, *NeuroD1* (MODY6), mitochondrial DNA.
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, somatostatinoma, aldosteronoma, others
E. Drug or chemical induced
Glucocorticoids, nicotinic acid, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, interferon, pentamidine, diazoxide
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. Gestational diabetes

treatment at some stage of their disease. Such use of insulin does not, of itself, allow for aetiological classification.

Type 1 diabetes, which accounts for only 5% of cases, includes that which results from pancreatic beta-cell destruction. These patients are prone to ketoacidosis, coma and death. Diabetes that is due to an autoimmune process and that for which the aetiology of beta-cell destruction is unknown [which includes latent autoimmune diabetes in adults (LADA)] is also classified as type 1diabetes.

Type 2 diabetes is the most common aetiological type (> 90% of cases) and is predominated by disorders of insulin action (insulin resistance), with insulin deficiency relative to a predominant secretory defect (i.e. disorders of insulin action and secretion).

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

Type 1 diabetes	Type 2 diabetes
Usually < 30 years, but not always	Usually older, but prevalence in children, adolescents and young adults increasing
Usually lean weight	Mostly overweight or obese, with acanthosis nigricans
Onset is acute	Onset is insidious/gradual
Almost always symptomatic (i.e. polyuria, polydipsia, weight loss)	Often asymptomatic
Prone to ketosis, often ketoacidotic at diagnosis	Not usually prone to ketosis, but ketoacidosis may be present at diagnosis
Diagnosis: usually has unequivocal hyperglycaemia	Diagnosis often during routine screening
Insulin necessary, as of diagnosis, for survival	Usually controlled with non-insulin therapies, or may need insulin for symptom control
Otherwise normally healthy	Often have co-morbidities* or diagnosed after emergency admission for myocardial infarction or stroke

*Comorbidities: e.g. hypertension, dyslipidaemia, sleep apnoea, fatty liver disease, polycystic ovary syndrome).

The clinical distinction between type 1 and type 2 diabetes can sometimes be difficult, particularly in adolescents and young adults. Table II highlights the clinical differences that may assist in making the distinction.

Other specific types of diabetes include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drugs (Table I).

Gestational diabetes refers to hyperglycaemia (glucose intolerance) with onset or first recognition during pregnancy.

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3. Diagnosis of diabetes mellitus and other disorders of glycaemia, and screening for diabetes mellitus

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Table I: Criteria for the diagnosis of diabetes and categories of intermediate hyperglycaemia

Diagnostic test	Impaired fasting glucose (IFG)	Impaired glucose tolerance (IGT)	Diabetes
Fasting plasma glucose (FPG)[a]	6.1-6.9 mmol/l	< 7.0mmol/l (if measured)	≥ 7.0 mmol/l; or
Two-hour plasma glucose (2-h PG) during oral glucose tolerance test (OGTT)[b]	< 7.8 mmol/l (if measured)	7.8-11.0 mmol/l	≥ 11.1 mmol/l; or
Glycated haemoglobin A_{1c} (HbA_{1c})[c]	-	-	≥ 6.5%; or
Random plasma glucose (RPG)[d]	-	-	≥ 11.1 mmol/l if classic symptoms of diabetes or hyperglycaemic crisis is present.

a: "Fasting" is defined as no caloric intake for at least eight hours.

b: The test should be performed as described by World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in 250 ml water ingested over five minutes.

c: Provided that the test method meets stringent quality assurance criteria, that the assay is standardised according to criteria aligned with the international reference values [National Glycohemoglobin Standardization Program (NGSP) -certified and standardised to the Diabetes Control and Complications Trial (DCCT) assay], and that there are no conditions present which preclude its accurate measurement (Tables II and III).

d: "Random" (casual) is defined as any time of day, without regard to time of last meal. The classic symptoms of hyperglycaemia include polyuria, polydipsia and weight loss. "Hyperglycaemic crisis" refers to diabetic ketoacidosis or hyperosmolar nonketotic hyperglycaemia.

3.1 Diagnosis of diabetes and other categories of glucose tolerance[1,2,3,4,5]

3.1.1 Criteria for the diagnosis of diabetes mellitus and other disorders of glycaemia

The various criteria and cutpoints used for the diagnosis of diabetes and the categories of intermediate hyperglycaemia are outlined in Table I.

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 obvious symptoms (i.e. polyuria, polydipsia and weight loss).

The diagnosis of diabetes should 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. For capillary blood glucose measurements, 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

During the development of this guideline, SEMDSA adopted and endorsed the abbreviated report of a WHO consultation on the use of HbA_{1c} in the diagnosis of diabetes mellitus.[5] However, the following conditions must be met before this HbA_{1c} can be used for diagnosis:

- The test method used must meet stringent quality-assurance criteria
- The assay must be standardised to criteria aligned with international reference values (i.e. NGSP certified).
- The assay must be standardised to the DCCT assay.
- There must be no conditions that preclude the accurate measurement of HbA_{1c} (Tables II and III).

Table II: Use of HbA_{1c} in the diagnosis of diabetes mellitus[5]

Diagnosis of diabetes	- $HbA_{1c} \geq 6.5\%$ - $HbA_{1c} < 6.5\%$ 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) - Accurate blood glucose measurement must generally be 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

Table III: Factors which influence HbA_{1c} measurement[5]

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	*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 HbA1c: 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

Some of these factors cannot be detected by certain assays

For a complete list of laboratories that are NGSP certified, the NGSP website can be consulted.[6] The WHO report[5] referred to now replaces the SEMDSA 2010 position paper on the topic.[7]

3.1.1.1 Diagnosis in symptomatic individuals and unequivocal hyperglycaemia (Table I)

In patients who have the classic symptoms of hyperglycaemia (i.e. 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. However, even severe hyperglycaemia detected under conditions of acute infective, traumatic, cardiovascular or other stress, may be transitory and should not be regarded as diagnostic of diabetes until confirmed subsequently.

3.1.1.2 Diagnosis in asymptomatic individuals or doubtful hyperglycaemia (Table IV)

Table IV: Diagnosis of diabetes in asymptomatic individuals and screening for diabetes (absence of unequivocal hyperglycaemia)

Testing methods: Either FPG, two-hour PG (OGTT) or HbA_{1c} Diagnosis requires confirmation with the same test method, but on another day.

Indications for 75 g OGTT:
- High-risk individuals (see Table V for risk factors)
- If, at initial testing
  - FPG: 5.6-6.9 mmol/l
  - RPG: 5.6-11.0 mmol/l (testing for FPG instead of OGTT also acceptable)
  - HbA_{1c}: 6.0-6.4% (possibly; no data available)

In asymptomatic individuals and in those about whom 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 (FPG or OGTT), *or* the HbA_{1c} test. If the test is abnormal, then the *same* test must be repeated on another day to confirm the diagnosis.

In the unlikely event that both a glucose-based test and the HbA_{1c} 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.

A test result below the diagnostic threshold for diabetes does not exclude the diagnosis of diabetes. So, despite the fact that the diagnostic cut-points for FPG are 7.0 mmol/l and 6.1 mmol/l for diabetes and IFG, respectively, one can only exclude the diagnosis of diabetes if the FPG is ≤ 5.6 mmol/l. The level of HbA_{1C} below which the diagnosis of diabetes can be excluded is not known. (The American Diabetes Assosciation uses a lower limit cut-point of 5.7%, but the WHO report does not endorse this.) This causes a dilemma in individuals in whom the HbA_{1C} test result is close to, but does not exceed, the diagnostic cut-point of 6.5%.

In any event, the OGTT is the preferred method of testing in high-risk individuals (Table V), and in those in whom the FPG does not allow the exclusion of diabetes. When RPG fails to exclude the diagnosis of diabetes (RPG = 5.6-11.0 mmol/l), either the OGTT or FPG should be measured for accurate diagnosis (Table IV). In the absence of an OGTT, a subjects glycaemic status remains uncertain because impaired glucose tolerance cannot be excluded.

3.2 Screening for type 2 diabetes in adults (Table V)

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 undergo glucose testing incidentally (*random screening*), to individuals identified as being at 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) who undergoes testing 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 healthcare setting. Community screening outside a healthcare setting (e.g. at 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 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.

Table V: Criteria for screening for type 2 diabetes in asymptomatic adults[a]

Indications	High-risk individuals: All adults (any age) with body mass index (BMI) ≥ 25 kg/m^2 (overweight or obese), plus one or more additional risk factors[b]: - Physical inactivity - Hypertension [blood pressure (BP) ≥ 140/90 mmHg] - Family history of diabetes (first degree) - Dyslipidaemia[c] - Polycystic ovarian syndrome - High-risk ethnic group e.g. those of South Asian descent - Cardiovascular disease history - Gestational diabetes or baby weighing > 4 kg - Previous IFG or IGT - Other conditions associated with insulin resistance If no risk factors: Age ≥ 45 years
Frequency	At three-year intervals, if normal More frequently, based on initial result and risk status (e.g. annually in those with IFG, IGT, or those with multiple risk factors)
Test method	FPG, two-hour PG (OGTT) or $HBA_{1c.}$ 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

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

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4. Organisation of diabetes mellitus care

As diabetes is a complex disorder, a systematic approach to the organisation of care is essential. There are a number of elements to this approach. These include: well trained and dedicated personnel, calibrated and functioning equipment, management and referral protocols, continuous supply of medication, a register of all patients to facilitate recall for non attendance and for specific aspects of regular care, legible patient records –flow charts and annual review carts are useful for following of clinical and biochemical measures. A process of regular audit with the implementation of interventions to improve care needs to be instituted.

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4.1 Requirements for a diabetes mellitus clinic

Table I outlines the requirements that need to be met for the establishment of a diabetes mellitus (diabetes) clinic.

4.2 Schedule of visits to a diabetes clinic

Table II provides a schedule of the history that must be elicited and examinations and investigation that need to be performed during visits to a diabetes clinic.

Table I: Requirements for a diabetes 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 or tuning fork - Glucometers in good working order - HbA1c 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 reaching targets for glycaemia, blood pressure (BP) and lipids - Numbers of patients receiving designated processes of care

Note that the frequency of examinations and tests are based on the assumption that the last set of observations was normal. In the presence of abnormalities, the frequency of examinations and tests must be increased.

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Table II: History, examination and special investigations recommended for visits to a diabetes clinic

	Initial visit	Three- to six-monthly visits	Annual visit
History			
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: Cardiovascular, neurological, bladder function, sexual function (i.e. erectile dysfunction), feet, visual, infection	X		X
Drugs			
- Current	X	Side-effects and adherence	X
- Allergies	X		X
Hypoglycaemic symptoms	X	X	X
Vaccinations			
- Pneumococcal (date)	X		X
- Influenza (date)	X		X
Lifestyle			
- Weight history	X		X
- Physical activity	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			
Weight	X	X	X
Height	X		X
Body mass index (BMI) (kg/m^2)	X	X	X
Waist circumference (cm)	X	X	X
Blood pressure (mmHg)	X	X	X

Table II (cont.): History, examination and special investigations recommended for visits to a diabetes clinic

	Initial visit	Three- to six-monthly visits	Annual visit
Feet			
- Inspection: Ulcers, soft tissue, deformities, Footwear	X	X	X
- Monofilament assessment	X		X
- Vibration sense using tuning fork, or pinprick sensation	X		X
- Ankle jerk	X		X
- Foot pulses	X		X
Oral cavity			
- Dental caries	X		X
- Gum disease	X		X
Eyes			
- Visual acuity	X		X
- Direct fundoscopy (dilated pupils), indirect fundoscopy, or fundus photographs	X		X[a]
Cardiovascular system	X		X
Injection sites, if appropriate	X	X	X
Special investigations			
Blood tests			
- Glucose	X	X	X
- HbA_{1c}	X	Six-monthly if at target, otherwise three-monthly. Also, whenever treatment is adjusted	X
- Lipids: Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides	X		X
- Creatinine, and calculate estimated GFR	X		X
- Potassium	X		X
- HIV	X		X
Urine			
- Glucose	X		X
- Ketones	X		X
- Protein (current g/lines albumin/creatinine ratio)	X		X
ECG: If known ischaemic heart disease, older than 45 years and other cardiovascular disease risk factors	X		X
Other important tasks			
Education: Self-management and lifestyle adjustment, including smoking cessation	X	X	X
Setting goals	X	X	X
Preconception counselling and family planning	X		X
Medication revision/adjustment	X	X	X
Immunisations	X		X

[a]Interval for retinopathy screening can be increased to once every 2 years if the last 2 examinations were normal; more frequent examinations are required in the presence of abnormalities.

5. Diabetes self-management education

"Diabetes is a chronic, manageable condition which requires major changes in lifestyle to optimize its management. Motivating behaviour change in diabetic patients is one of the most important, but also more frustrating experiences, for general practitioners." Bob Mash

Diabetes self-management education (DSME) is the cornerstone of care for all individuals with diabetes mellitus who want to achieve successful health-related outcomes, whilst learning coping skills. Education promotes compliance or adherence by utilizing motivational and behavioural strategies in an effort to guide patients to change.

The literature supports a strong core group of topics in the design of the curriculum for teaching self-management, through an evidence-based, structured programme delivered by informed educators. This should be available to all people with diabetes, irrespective of culture, race, language or socio-economic status. Sufficient time and resources should be made available in order to do this effectively.

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5.1 General principles of diabetes self-management education

- An evidence-based, structured education programme should be offered to all patients at the time of diagnosis, and consolidated at regular intervals thereafter. The aim is to promote patient self-management.
- The programme should be presented by educators who have been appropriately trained, particularly in motivational interviewing.
- The programme should be available to all people with diabetes, irrespective of language, ethnicity, culture, educational level, or socioeconomic status.
- Diabetes self-management education (DSME) should be adapted for the elderly, the handicapped and people who live alone.
- Specialised pre-conception education and care should be offered to improve pregnancy outcomes.
- Small-group education is the most cost-effective option. In order to bring about a glycated haemoglobin A_{1c} (HbA_{1c}) reduction of 1%, 23.6 hours of education are required.
- Educators should ensure that active learning is taking place.
- Psychological and emotional assessment is needed at regular intervals.
- A regular audit of the programme and its effect on outcomes is advised.

5.2 Topics to be covered by diabetes self-management education

- Basic knowledge of diabetes
- Importance of good comprehensive control and methods to achieve this.
- Insulin injection techniques and sites of injection
- Self-monitoring of blood glucose
- Recognition and management of acute and chronic complications
- Foot care
- Smoking cessation and responsible alcohol use
- Pre-conception care:
  - Refer to the section "Diabetes in pregnancy"
- Pregnancy: preparing, managing diabetes during pregnancy and appropriate postnatal care
- Psychosocial issues, stress management and coping skills
- Training of caregivers and family of people with diabetes
- Managing diabetes emergencies.
- Importance of an identification disc or bracelet
- Children with type 2 diabetes should be referred for specialist assessment and diabetes education
- Management of elderly patients:
  - Assess knowledge and understanding of diabetes - evaluate ability to learn and apply new self-

care skills
- Asses nutrition and physical activity
- Address poly-pharmacy and co-morbidities
- Assess for cognitive dysfunction, depression and physical disability
- Address quality of life versus life expectancy

5.3 Diabetes educators

There is a major shortage of diabetes educators throughout South Africa. The reasons for this include the lack of appropriately accredited courses as well as the lack of appropriate remuneration for diabetes educators. Universities and nursing colleges are encouraged to develop a diabetes educators' curriculum and accredited courses. In the absence of such courses, a DESSA (Diabetes Education Society of South Africa) and SEMDSA approved course should be recognised for accreditation. Diabetes educators should be reimbursed appropriately.

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6. Medical nutrition therapy

Medical nutrition therapy (MNT) is important for the prevention, treatment and self-management of diabetes, and the prevention or delay in onset of diabetes-related complications. MNT can reduce HbA_{1c} by 1-2%, depending on the duration of diabetes.

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6.1 Key components of medical nutrition therapy

Weight loss is an important therapeutic intervention in obese and overweight individuals with type 2 diabetes Individuals with type 2 diabetes should be encouraged to implement the healthy lifestyle changes, including reducing the calorie intake, consuming less saturated fats, trans fats, cholesterol and sodium, and increasing physical activity. These measures are all part of an effort to improve blood glucose control, dyslipidaemia and blood pressure.

Consistent carbohydrate intake and an even and regular distribution of meals may help to control blood glucose levels and weight.

Plasma glucose monitoring can be used to determine if medical nutrition therapy (MNT) is effective in achieving blood glucose targets.

Restrictive diets and fad diets ("carb-free", "high-protein", "fat-free", very low calorie diets etc.) should be avoided as they offer no long term benefit over conventional healthy eating plans. Evidence suggests that commercial weight-loss programs that follow healthy-eating principles can also be an effective strategy for weight-loss.

MNT involves the following:

- Following a patient-centred approach.
- Assessing the patient's nutritional status and diabetes self-management knowledge and skills.
- Identifying and negotiating individualised nutrition goals.
- Tailoring the nutritional intervention, so that there is a careful match of both a meal-planning approach and educational materials with the patient needs, and so that there is still some allowance for flexibility.
- Evaluating outcomes, and ensuring that there is ongoing monitoring, support and assessment.

Table I summarises MNT for type 2 diabetes.

The FDA has established an acceptable daily intake (ADI) for each sweetener (Table I). This is the maximum amount considered safe to consume each day, over the course of a lifetime.

Table I: Summary of MNT for type 2 diabetes

A. Follow a healthy, balanced eating plan

- Eat a variety of fresh fruit and vegetables every day, but avoid fruit juices
- At least half of the grain intake must be from wholegrain products
- Consume low-fat dairy products and soya beverages fortified with calcium
- Use a variety of meat alternatives, including pulses, soya and tofu
- Consume fish at least twice per week
- Limit the intake of processed and convenience foods
- Increase the intake of water to meet daily fluid requirements

B. Carbohydrates

- Carbohydrates should make up 45-60% of the total energy intake
- Monitoring carbohydrate intake , whether by carbohydrate counting, exchanges or experienced-based estimation, remains a key strategy in achieving optimum glycaemic control
- The use of glycaemic index and glycaemic load may provide a modest an additional benefit compared to considering only total carbohydrate content
- Limit the intake of sugar alcohols (maltitol, mannitol, sorbitol, lactitol, isomalt, xylitol) to < 10 g per day
- A sucrose intake of up to 10% of total energy intake per day is acceptable
- Limit the total fructose intake to 60g per day
- Increase the intake of soluble and insoluble fibre to 25-50 g per day
- The use of artificial sweeteners, including acesulfame-K, aspartame, saccharine and sucralose, are safe when consumed within the daily limits established by the FDA

C. Protein

- Proteins should make up 15-20% of the total energy intake
- 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
- In type 2 diabetes, ingested protein can increase the insulin response without increasing plasma glucose levels; therefore, protein should not be used in the treatment and prevention of hypoglycaemia

D. Fat

- The fat intake should be restricted to < 35% of the total energy intake
- The saturated fat intake should be restricted to < 7% of the total energy intake
- The polysaturated fat intake should be restricted to < 10% of the total energy intake
- Minimise the intake of trans-fats
- Consume monounsaturated fat and omega-3 fatty acids from both plant (flaxseed, walnuts, and canola) and marine (fatty fish) sources instead of saturated fat.
- Two more servings of fish per week will provide the recommended omega-3 polyunsaturated fatty acids

E. Salt

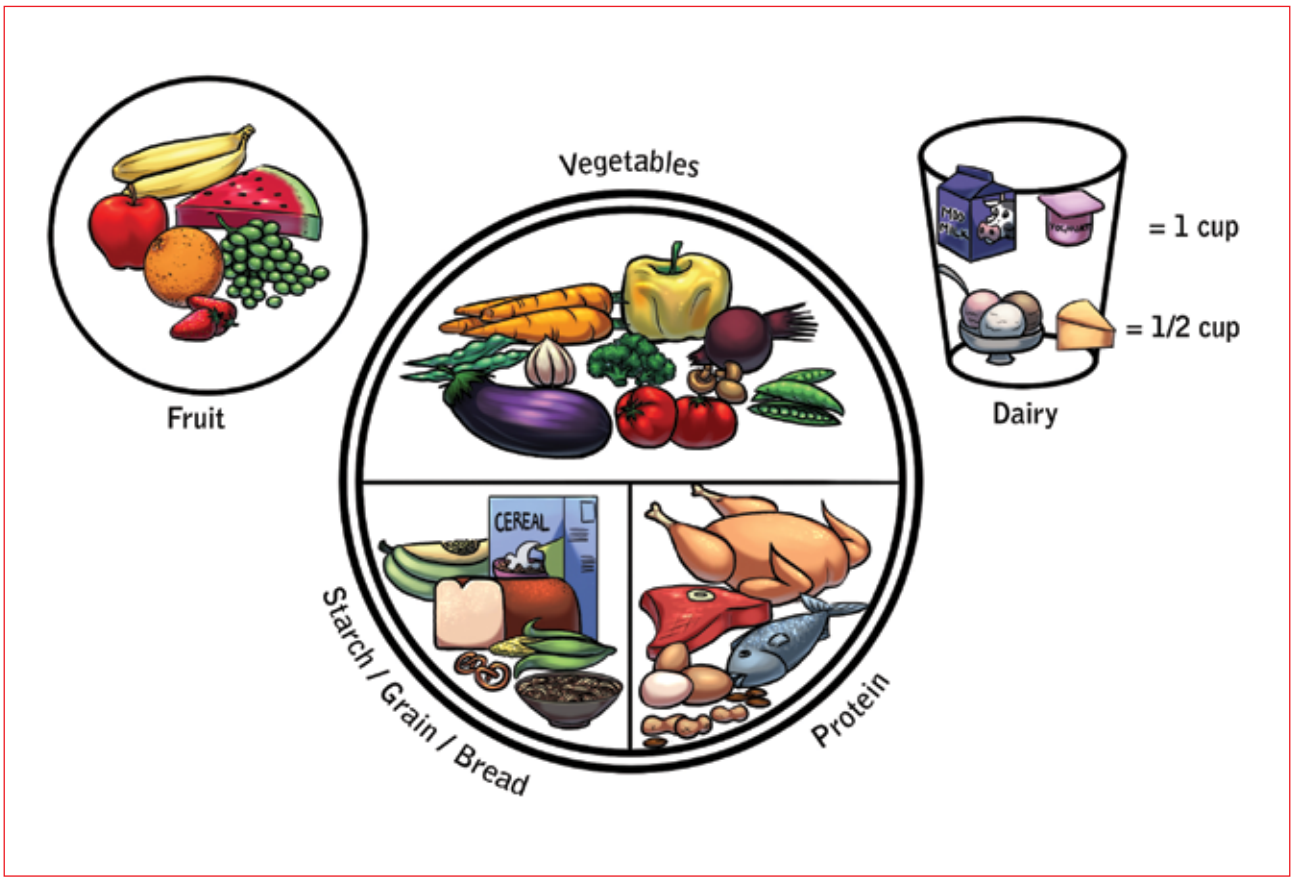
- The main source of sodium in the diet is the salt contained in packaged and processed foods and in foods from restaurants. Consumption of these products should be limit or avoided altogether.
- Reducing dietary sodium to < 2 300 mg per day may help to control blood pressure.

F. Vitamins and minerals

- There is no clear evidence for routine mineral and vitamin supplementation in individuals with type 2 diabetes, except for vitamin D supplementation in those older than 50 years
- Mineral and vitamin supplementation may be needed in selected groups, such as the elderly, lactating and pregnant women, and vegans
- Routine antioxidant supplementation, including vitamin E, vitamin C and beta carotene, is not recommended, because of insufficient evidence of efficacy and concerns related long-term safety; supplementation may be considered in smokers
- The benefits of chromium supplementation in individuals with diabetes has not been clearly demonstrated, and therefore cannot be recommended

G. Alcohol

- Adults who choose to consume alcohol should do so in moderation: one unit per day or less for women, and two units per day or less for men
- Moderate alcohol consumption, with food, does not cause acute hyperglycaemia or hypoglycaemia.
- Individuals on insulin or insulin secretagogues should be aware of the risks of delayed hypoglycaemia (for up to 24 hours after consumption); alcohol should be consumed with food to reduce the risk of hypoglycaemia



6.2 The healthy diabetes plate

The Idaho Plate Method is a good starting point for healthy meal planning, that can be utilised until referral to a dietitian for MNT. This plate model replaces the food pyramid as a meal planning tool.

The plate model is effective for both managing diabetes and losing weight. It enables patients to choose the foods they enjoy, but within the recommended portion sizes. The focus should be on increasing the portion sizes of non-starchy vegetables, and decreasing the portion sizes of starches. Using an image of a plate with illustrated portion sizes encourages patients to consume carbohydrate throughout the day, which will assists with blood glucose control.

6.2.1 How to use a plate model

- Mark a line down the centre of a 22 cm-plate.
- Divide the one half of this plate into two equal sections.
- Fill the undivided half of the plate with a variety of non-starchy vegetables, such as spinach, carrots, lettuce and other greens, cabbage, green beans, broccoli, cauliflower, tomatoes, cucumber, beets, mushrooms and peppers.
- Fill one of the quarter sections with starchy foods, such as whole-grain breads (e.g. whole-wheat or rye), whole-grain high-fibre cereal, cooked cereal (e.g. oatmeal), brown or long-grain rice, pasta, baby potatoes, green peas, sweet potatoes, whole-grain crackers and fat-free popcorn.
- Fill the last quarter of the plate with meat and meat substitutes, such as skinless chicken and turkey portions, fish and other seafood, lean cuts of beef and pork (e.g. sirloin, fillet or pork loin), tofu, soya, eggs and low-fat cheese. Avoid processed meats (e.g. salami, Vienna sausages and polony), which are high in fat and salt.
- Add a glass (240 ml) of non-fat or low-fat milk, or 180 ml of light yoghurt. Eat or drink at least two servings per day.
- Add a medium portion of fruit (e.g. oranges, apples, pears or small bananas), or two small fruits (e.g. plums or peaches), or three quarters of a cup of fresh fruit salad. Instead of eating fruit with meals, these can be used as snacks between meals. Keep to two or three servings per day.

7. Physical activity and type 2 diabetes mellitus

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

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7.1 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[1] and type 2[2] diabetes mellitus.

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.[3-5]

People with type 2 diabetes will derive the following benefits from regular physical activity:[6-8]

- 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.

7.2 Physical activity counselling

Structured physical activity counselling provided by specialist physicians, general practitioners, skilled healthcare personnel or case managers has been very successful in increasing physical activity.

People with type 2 diabetes should be advised to perform at least 150 minutes per week of moderate-intensity aerobic physical activity (50-70% of maximum heart rate) (Table I) and, in the absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance training three times per week (Table II).[2]

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

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[2]

Definition	Frequency	Examples
Activities that require muscular strength to move a weight or work against a resistance load[a]	Two to three times per week: Start with one set of 10-15 repetitions at moderate weight Progress to two sets of 10-15 repetitions Progress to three sets at heavier weights	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

7.3 Evaluation before recommending an exercise programme

Patients with multiple cardiovascular risk factors for coronary artery disease should be assessed before an exercise programme is recommended.[6] Certain conditions might be contraindications to certain 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.

7.4 Hypoglycaemia

In individuals taking insulin and/or insulin secretagogues, physical activity can cause hypoglycaemia if the medication dose or carbohydrate consumption is not altered.[5] This is particularly so at times when exogenous insulin levels are at their peaks and if physical activity is prolonged. Additional carbohydrate should be ingested if pre-exercise glucose levels are < 6.6 mmol/l.

Snack size and insulin dosage reductions must be individualised for each patient, as no recommendations are available. Blood glucose measurements before, during and after exercise will aid in the management of snack size and insulin dosage adjustments.

Supplementary carbohydrates are generally not necessary for individuals treated only with metformin or alpha-glucosidase inhibitors without insulin or secretagogues.

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8. Assessment of glycaemic control

The primary purpose in treating glycaemia in patients with type 2 diabetes mellitus is to reduce blood glucose sufficiently to prevent or delay the onset of microvascular, and perhaps macrovascular, complications. In order to achieve these goals, it is essential to set targets for both short- and long-term control. Without having set targets, it is likely that patients will be undertreated and the aims of appropriate therapy will not be achieved. This section outlines appropriate targets for long-term glycaemic control [glycated haemoglobin (HbA_{1c})], and the appropriate blood-glucose levels needed to attain those targets.

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8.1 Targets for glycaemic control

8.1.1 HbA_{1c} targets

There is a strong epidemiological evidence base for selecting a target glycated haemoglobin A_{1c} (HbA_{1c}) level of < 7%.[1-4] Patients with type 2 diabetes mellitus (diabetes) with HbA_{1c} levels > 7.5% have a 2.5- to 5-fold greater relative risk of developing microvascular complications,[5,6] and a fivefold greater risk of developing peripheral artery disease.[6]

Both the International Diabetes Federation (IDF) and the American College of Endocrinology (ACE) have recommended a target HbA_{1c} level < 6.5%. However, there is little evidence that, by aiming for such a low target, particularly in patients with long-standing diabetes, cardiovascular outcomes will improve. The ADVANCE study (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) is the only prospective trial to date to show a reduction in microvascular disease after reducing the HbA_{1c} to < 6.5%.[7]

In the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes), the results suggest that study patients who had not had a previous cardiovascular event and in whom glycaemic control had been intensified to achieve HbA_{1c} levels below 6.5%, the so-called "intensively treated group", may have had a lower risk of cardiovascular events.[8] In an intensive control subgroup of the VADT trial (Veterans Affairs Diabetes Trial), patients who had less coronary artery calcification also seemed to have a reduced cardiovascular event rate when compared with those with more coronary artery calcification.[9]

HbA_{1c} targets must clearly be individualised:

- In newly diagnosed patients and those without cardiovascular disease, an HbA_{1c} target < 6.5% may be a feasible and reasonable aim.
- In the elderly, the infirm, those with limited life expectancy or those with hypoglycaemic unawareness, a target < 7.5% (or even up to 8.0%) may be acceptable.
- In the majority of patients, an HbA_{1c} target < 7% seems reasonable.

8.1.2 Blood glucose targets

8.1.2.1 Fasting plasma glucose

The "normal" fasting plasma glucose (FPG) is accepted as < 6.1 mmol/l. However, a meta-analysis of 38 prospective studies has found an association of increased risk of cardiovascular events with FPG > 5.5mmol/l.[10] However, the DECODE study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) suggested that FPG < 7.0 mmol/l indicates a low risk of cardiovascular disease.[11]

Overall, a fasting or preprandial target of 4.0-7.0 mmol/l is recommended.[12]

8.1.2.2 Postprandial glucose

In nondiabetic individuals, peak postprandial glucose (PPG) generally does not exceed 7.8 mmol. However, the DECODE study has demonstrated a linear relationship between the post-glucose load glucose level and cardiovascular disease, with no "lower" limit cut-off.[12] The ACE[13] and the IDF[14] recommend a PPG target < 7.8mmol/l, while the American Diabetes Association (ADA) recommends a PPG target ≤ 10mmol/l.[15]

The actual target to be aimed for will depend on the target HbA_{1c} (Table I).

Table I. Targets for HbA_{1c}, fasting plasma glucose and postprandial glucose in different patient types

Patient type	Target HbA_{1c}	Target FPG	Target PPG
Young Low risk Newly diagnosed No cardiovascular disease	< 6.5%	4.0-7.0 mmol/l	4.4-7.8 mmo/l
Majority of patients	< 7%	4.0-7.0 mmol/l	5.0 -10.0 mmol/l
Elderly High risk Hypoglycaemic unaware Poor short-term prognosis	< 7.5%	4.0-7.0 mmol/l	< 12.0 mmol/l

8.2 Monitoring of glycaemic control

8.2.1 Monitoring of HbA_{1c}

If the patient's HbA_{1c} is at target and the treatment has not been altered, the HbA_{1c} can be checked every six months.[16]

If HbA_{1c} is above the target or the treatment has been altered or intensified, the HbA_{1c} after three months.[17]

8.2.2 Self-monitoring of blood glucose

8.2.2.1 Individuals on insulin

Self-monitoring of blood glucose (SMBG) is essential, but the frequency depends on the insulin regimen being used:

- In those individuals injecting insulin two to four times injections per day, testing should be undertaken at least three times per day.[18,19]
- In those individuals on once-daily insulin, with or without oral hypoglycaemic agents, once-daily testing at variable times is recommended.

8.2.2.2 Individuals on oral hypoglycaemic agents

Evidence is conflicting, and there are numerous publications discussing the advantages and disadvantages of SMBG in patients being treated with oral hypoglycaemic agents.[20-22] However, in those who were recently diagnosed, SMBG[23] and structured testing combined with appropriate patient education has been shown to be of benefit.[24-26]

In 2009, the IDF advised that SMBG should only be undertaken by patients who have been taught how to incorporate the testing into their diabetes care plan.[20] The decision to self-monitor blood glucose should be undertaken at the time of diagnosis, as ongoing SMBG may assist patients in understanding and participating in their care. However, SMBG protocols should be individualised, and the purpose of SMBG should be agreed upon by the patient and the healthcare provider

Recommendations for patients on oral agents

- SMBG should only be considered in patients on oral hypoglycaemic agents if adequate patient education accompanies initiation of testing.
- For most patients, three to five tests per week should be sufficient.
- Testing must be structured and have meaning for the patient.
- Patients must understand their glycaemic targets, and know what to do if these are not being achieved.

8.2.2.3 Circumstances demanding more frequent SMBG

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

8.2.3 Continuous glucose monitoring (CGM)

CGM is a supplemental tool to SMBG and is indicated in the following circumstances:

- Patients with hypoglycemia unawareness.
- Patients with frequent hypoglycaemic episodes.
- Patients with discrepant HbA1c and SMBG results
- For additional monitoring during pregnancy

8.3 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, and 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: Translating HbA1c into eAG

HbA1c (%)	eAG (mmol/l)
6	7.0
7	8.6
8	10.2
9	11.8
10	13.4
11	14.9
12	16.5

When the HbA1c/eAG and measured blood glucose (laboratory or SMBG) appear discrepant, clinicians should consider the possibility of haemoglobinopathy, altered red-cell turnover, or assay interference. In these circumstances, CGM or other measures of chronic glycaemia, such as fructosamine, should be considered.

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9. Glucose control: Non-insulin therapies

Patient and clinician acceptance make non-insulin-based therapies the backbone of type 2 diabetes management. In an attempt to delay and even avoid insulin therapy, innovative oral agents are being developed. New information also continues to accumulate about the older agents.

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The essential information relating to non-insulin therapies in type 2 diabetes is summarised in Table II under section 11 "Glycaemic control: The 2012 SEMDSA treatment algorithm". The text in this section is provided for additional explanation and reading.

9.1 Metformin

Metformin was isolated from *Galega officinalis* (goats rue), which was used to treat symptoms characteristic of diabetes mellitus in medieval times. The plant extract, however, was found to be toxic in studies carried out in the early 1920s. Metformin, as we know it, was developed in the 1950s, together with the other biguanides, phenformin and buformin. However, owing to the common occurrence of lactic acidosis with the others, metformin is now the only biguanide that is commercially available.

9.1.1 Mechanism of action

Metformin exerts its effect by activating adenosine monophosphate (AMP) kinase, resulting in reduction of hepatic glucose production via multiple intracellular pathways. Additional effects that have been described include improved peripheral glucose utilisation, reductions in gastrointestinal glucose absorption, enhanced incretin responses, improvements in free fatty acid metabolism, lipid profiles, vascular and endothelial function and a reduction in cancer mortality.

9.1.2 Efficacy

Metformin is now well established as the primary "anchor" oral anti-diabetic agent in the management of type 2 diabetes. It is the only drug with proven efficacy in reducing cardiovascular outcomes and mortality as a primary endpoint in a randomised controlled trial (UKPDS 34). In this study, patients assigned to intensive blood glucose control with metformin had a significant 32% lower risk of developing any diabetes-related endpoint than patients assigned to conventional diet treatment. The metformin group also had significantly greater risk reduction than the group assigned to intensive therapy with a sulphonylurea or insulin. It is not widely known, though, that metformin did not demonstrate any significant microvascular benefits compared to conventional diet treatment, and this remained so in the post-trial monitoring follow-up study.

When used as monotherapy, metformin can reduce HbA_{1c} by 1-2%.

9.1.3 Dosing

The minimum effective dose of metformin is 500 mg once daily, and the optimal dose is about 2 000 mg per day in two or three divided doses, although some patients derive additional benefit from doses up to 2 550 mg per day.

9.1.4 Adverse effects and contraindications

About 30% of users will report gastrointestinal side-effects (e.g. diarrhoea, cramping, bloating and flatulence). These can be minimised by titrating the dose gradually over one or two months, or by temporarily discontinuing the drug before reintroducing it. Fewer than 10% of patients will need to discontinue the drug permanently because of gastrointestinal intolerance. In this circumstance, because it is desirable to retain the metformin molecule, the extended-release formulation of metformin should be prescribed instead of switching to another class of drug.

Lactic acidosis with metformin is now known to be rare (0.05 cases/1 000 patient years), and most of these cases occur in the context of inappropriate usage.

However, widespread usage and experience have shown that metformin is a useful drug, even in conditions where it is supposedly contraindicated. So, despite the contraindication in liver disease, metformin can actually improve liver function in patients with non-alcoholic fatty liver disease. Also, the Food and Drug

Table I: Traditional contraindications to metformin use

Renal dysfunction
Severe liver disease
Use of intravenous contrast media
Major surgical procedures
Congestive heart failure
Acute myocardial infarction
History of lactic acidosis
History of alcohol abuse

Administration (FDA) in the United States has withdrawn the heart failure contraindication based on publications of improved outcomes in heart failure patients on metformin. And metformin has shown some benefit compared to insulin and sulphonylureas in the aftermath of acute myocardial infarction (DIGAMI-2) study.

Not surprisingly, then, many surveys have shown that metformin remains in use at the time of contraindications confirming a lack of respect for the current licensing guidance. This has been most obvious in patients with renal impairment, where its continued use has reassuringly not been associated with adverse outcomes. Accumulated data on metformin usage in renal impairment has led to a relaxation of the guideline here (Table II). Notwithstanding the better than expected adverse event profile with metformin, It remains important to follow prescribing recommendations and to remain vigilant against a too casual approach to using metformin.

9.1.5 Metformin in the 2012 SEMDSA treatment algorithm

At step 1, as monotherapy, metformin is the initial therapy of choice and should be started at the time of diagnosis in all patients (overweight and normal weight), unless specifically contraindicated. It is recommended that metformin therapy continue even when other classes of (including insulin) are added subsequently.

At step 2, metformin can be added as a second-line agent in patients where treatment has been initiated with any other class of drug.

9.2 Sulphonylureas

Sulphonylurea drugs have been used in the treatment of type 2 diabetes mellitus (diabetes) since the 1950s.

9.2.1 Mechanisms of action

These drugs induce insulin release by binding to specific receptors on the pancreatic beta cell-K_{ATP} channel. The beta cell-K_{ATP} channel is a hetero-octamer, comprising a potassium channel (Kir6.2) and a sulphonylurea receptor (SUR1). The binding of sulphonylureas to SUR1 leads to glucose-independent closure of the potassium channel, membrane depolarisation, the opening of calcium channels, and the release of stored insulin. Sulphonylureas may have additional effects, including decreasing growth-hormone secretion, and there is experimental evidence of increased lipogenesis and glycogen synthesis.

Table II: Metformin use 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
45-60 ml/minute/1.73 m^2	- Continue use - Increase monitoring of renal function (every three to six months)
30-45 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**

Sulphonylurea drugs available in South Africa include glibenclamide, gliclazide, glipizide, glimepiride and chlorpropamide (no longer in clinical use). These drugs are compared in Table III.

9.2.2 Efficacy

The clinical efficacy of sulphonylurea drugs has been demonstrated in many studies, including the United Kingdom Prospective Diabetes Study (UKPDS). The reduction in glycated haemoglobin A_{1c} (HbA_{1c}) ranges from 1.5 to 2.0%, with similar efficacy amongst the different sulphonylureas. Furthermore, the UKPDS showed significant reduction in microvascular complications of diabetes with sulphonylurea therapy. More recently, ADVANCE study showed that modified-release gliclazide significantly reduced microvascular complications in a large cohort of subjects with type 2 diabetes and risk factors for vascular disease. By contrast, macrovascular disease was neither reduced nor worsened in the ADVANCE study.

Table III: Comparison of the pharmacokinetic profiles of sulphonylurea drugs

	Glibenclamide	Gliclazide	Glimepiride	Glipizide
Protein binding	99%	96%	>99%	>90%
Peak concentration (hours)	3-4	3-4	2-3	2.5
Elimination $t_{½}$ (hours)	10	10-12	5-8	2-4
Metabolism	CYP2C9	CYP2C9	CYP2C9	CYP2C9
Excretion of metabolites	50% renal 50% GIT	60-70% renal 10-20% GIT	60% renal 40% GIT	-
Duration of hypoglycaemic effect (hours)	16-24	24	16-24	12-24

9.2.3 Dosing

- Glibenclamide: Starting dose 2.5 mg once daily; maximal dose 15 mg daily. Doses exceeding 10 mg per day to be given in two divided doses.
- Gliclazide: Starting dose 40 mg once daily; maximal dose 320 mg daily. Doses exceeding 80 mg per day to be given in two divided doses.
- Gliclazide modified-release: Starting dose 30 mg once daily; maximal dose 120 mg once daily.
- Glimepiride: Starting dose 1 mg daily; maximal dose 6 mg once daily.
- Glipizide: Starting dose 2.5 mg once daily; maximal dose 40 mg daily. Doses exceeding 15 mg per day to be given in two divided doses.

9.2.4 Adverse effects and contraindications

Concern that sulphonylurea drugs may worsen cardiovascular outcome derives from the University Group Diabetes Program, in which tolbutamide was used. Subsequent studies have examined the role of sulphonylurea drugs binding to cardiac SUR receptors and the possibility of reduction in ischaemic pre-conditioning as an explanation for varied cardiac outcomes with different agents. There is evidence that glipizide, gliclazide and glimepiride bind the cardiac SUR less avidly than glibenclamide. A French study showed that prior treatment with glibenclamide was associated with increased mortality and increased rate of complications in subjects with type 2 diabetes after acute myocardial infarction, as compared to prior treatment with gliclazide or glimepiride.

The major adverse effects of sulphonylureas include weight gain and hypoglycaemia. Weight gain has been demonstrated in numerous studies. The UKPDS reported a mean weight gain of 5.3 kg over the first six years of the study, with most of the weight gain occurring in the first year of treatment. Lesser degrees of weight gain have been reported with gliclazide and glimepiride.

Hypoglycaemia is the most serious adverse effect of therapy with sulphonylurea drugs. The incidence of sulphonylurea drug-induced hypoglycaemia in South Africa is unknown. In the first 10 years of the UKPDS, hypoglycaemia (of any severity) occurred in 11% of patients per year treated with chlorpropamide, 17.7% treated with glibenclamide, and 36.5% treated with insulin. A number of studies have shown higher rates of hypoglycaemia with glibenclamide than with other second-generation sulphonylureas. This observation is possibly related to the long duration of action of glibenclamide, as well as the hypoglycaemic activity of both primary metabolites (4-trans-hydroxy-glibenclamide and 3-cis-hydroxy-glibenclamide). One study showed the incidence of severe hypoglycaemia with glibenclamide to be 5.6/1 000 person years, compared to 0.86/1 000 person years in subjects treated with glimepiride. Gliclazide has also been shown to be associated with less hypoglycaemia than glibenclamide. Glimepiride and glipizide appear to have similar hypoglycaemic-potential. The GUIDE study compared gliclazide-modified release with glimepiride and showed that both drugs were equally efficacious but gliclazide-modified release had a significantly lower rate of hypoglycaemia. Significant risk factors for severe sulphonylurea-induced hypoglycaemia include renal impairment, advanced age and polypharmacy.

9.2.4.1 Contraindications to sulphonylurea use

- Brittle or unstable diabetes.
- Type 1 diabetes.
- Renal impairment: Glibenclamide is absolutely contraindicated if eGFR has not been measured in the preceding year, or if it is < 60 ml/minute/1.73m^2. Doses of gliclazide, glimepiride and glipizide may need to be reduced in renal impairment. No dose adjustments are recommended for gliclazide modified-release with renal impairment.
- Severe liver dysfunction.
- Allergy to sulphonamides or sulphur.
- Caution in elderly subjects.
- Caution in porphyria.
- Caution in lactation.

9.2.5 Sulphonylurea drugs in the 2012 SEMDSA treatment algorithm

Sulphonylureas are retained as a therapeutic option. The use of glibenclamide is strongly discouraged, other than in gestational diabetes, if the decision is taken to treat this condition with a sulphonylurea.[22] In all other instances, preference should be given to other second-generation sulphonylurea drugs. In making this recommendation the Guideline Committee and other experts considered their collective experience with regards to glibenclamide-induced severe hypoglycaemia, as well as the lack of renal function testing for a significant (if not the majority) of South Africans with diabetes. Notwithstanding the lack of formal studies, the committee felt that there are too many patients who present to hospitals with undiagnosed renal failure and inappropriate glibenclamide therapy in both the public and private health care sectors. We therefore propose that glibenclamide therapy be phased out in favour of the other second generation sulphonylureas. We recommend that in the meantime, pharmacists should not dispense glibenclamide without the patient having record of a valid estimated glomerular filtration measurement > 60ml/min/1.73m^2 from the preceding 12 months.

9.2.5.1 Indications for second-generation sulphonylureas (glibenclamide not preferred)

- Step 1: Monotherapy at diagnosis in persons intolerant of metformin, or in normal-weight individuals or those

with marked symptoms of hyperglycaemia.

- Step 2: Added to metformin, basal insulin, a glucagon-like peptide-1 (GLP-1) agonist, or a dipeptidyl peptidase-4 (DPP-4) inhibitor.
- Step 3: Triple therapy with metformin and basal insulin, or metformin and an incretin.
- In gestational diabetes, glibenclamide is the sulphonylurea of choice (for specialist use only).

9.3 Alpha glucosidase inhibitors

9.3.1 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.

9.3.2 Efficacy

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 result in HbA_{1c} reductions of 0.8%, 0.9% and 0.5%, respectively.

In all studies, acarbose significantly reduced postprandial glucose (2.3-3.5mmol/l), and caused statistically significant weight loss or was weight neutral.

9.3.2.1 Cardiovascular effects

The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) 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.

9.3.3 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.

9.3.4 Adverse effects

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.

Acarbose does not cause hypoglycaemia when used as monotherapy, but may aggravate hypoglycaemia caused by sulphonylureas and insulin.

9.3.5 Acarbose in the 2012 SEMDSA treatment algorithm

The indications for acarbose in the SEMDSA algorithm are identical to those for DPP-4 inhibitors (Table VI).

INCRETINS

Incretins are gut hormones that are secreted from enteroendocrine cells into the blood within minutes after eating. One of their many physiological roles is to increase of insulin secretion and suppress glucagon secretion from the beta and alpha cells of the pancreas respectively, after eating. The net effect 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. These effects of incretins have made them suitable targets for pharmacological development.

The incretin effect

According to the incretin effect, oral glucose has a greater stimulatory effect on insulin secretion than intravenous glucose. This is mediated by several gastrointestinal peptides, particularly glucagon-like peptide-1 (GLP-1). 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 (diabetes). Endogenous GLP-1 has a short half-life of one to two minutes, as a result of rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). GLP-1 levels can be raised therapeutically by the use of injectable GLP-1 agonists that are resistant to enzymatic degradation, or by oral DPP-4 inhibitors (DPP4), which inhibit the degradation of endogenous GLP-1. When used alone, incretin mimetics do not cause hypoglycemia, because the effect on insulin and glucagon secretion is glucose dependent.

9.4 Dipeptidyl peptidase-4 inhibitor (gliptins)

9.4.1 Mechanism of action

In animal models, GLP-1 stimulates beta-cell proliferation and differentiation, and reduces apoptosis. However, the potential to positively impact on beta cell survival in humans has not been proven.

9.4.2 Efficacy

The DPP-4 inhibitors appear to have similar efficacy, and will reduce HbA_{1c} modestly, by 0.5-1.1%, when compared to placebo.

9.4.3 Dosing

The DPP-4 inihibitors include linagliptin, saxagliptin, sitagliptin and vildagliptin. These drugs are taken orally most are given once daily. No dose titration is necessary. Table IV provides a summary of the doses of the DPP-4 inhibitors.

9.4.4 Adverse effects and contraindications

DPP-4 inhibitors appear to have a good safety profile in short-term studies (6-24 months), where the majority of monotherapy studies reveal a safety profile comparable to that of placebo. They do not cause weight gain or hypoglycaemia, except when combined with other drugs capable of causing hypoglycaemia. DPP-4 inhibitors can be used in elderly patients without dose adjustments.

Uncommon potential adverse events include:

- Nasopharyngitis
- Urinary tract infections
- Lymphopenia
- Pancreatitis
- Hypersensitivity skin reactions.

9.4.5 DPP-4 inhibitors in the 2012 SEMDSA treatment algorithm

The clinical use of DPP-4 inhibitors is summarised in Table V.

Table IV: Doses of DPP-4 inhibitors

DPP-4 inhibitor	Recommended dose	Renal impairment	Hepatic impairment
Linagliptin[a,b]	5 mg once daily	No dose adjustment	No dose adjustment
Saxagliptin[c]	5 mg once daily	eGFR < 50 ml/minute: use 2.5 mg once daily	Contraindicated in moderate to severe disease
Sitagliptin[a]	100 mg once daily	eGFR < 50 ml/minute: use 50 mg once daily eGFR < 50 ml/minute: use 25 mg once daily	Contraindicated in severe disease
Vildagliptin	50 mg twice daily (once daily with sulphonylureas)	Contraindicated	Contraindicated in moderate to severe disease

a: No registration in South Africa at time of publication (March 2012)
b: Linagliptin should not be used if the patient is being treated with a P-glycoprotein or cytochrome (CY) P3A4 inducer, e.g. rifampicin
c: The dose of saxagliptin requires adjustment if taken concurrently with a strong CYP3A4/5 inhibitor, e.g. ketoconazole, itraconazole, indinavir, nelfinavir, ritonavir, saquinavir

Table V: Acarbose and DPP-4 inhibitors in the 2012 SEMDSA treatment algorithm

Absolute contraindications
- There is a compelling indication for insulin therapy - History of a serious hypersensitivity reaction to DPP-4 inhibitors. - Patients with a history of acute pancreatitis, chronic or recurring pancreatitis and those with pancreatic cancer.
Indications for DPP-4 inhibitors or acarbose
At Step 3: Add-on therapy as part of an oral three-drug regimen (must meet all criteria) ☐ Inadequate glycaemic control with combination therapy with maximally tolerated doses of metformin and sulphonylureas, **and** ☐ Patient is a poor candidate for insulin therapy (See Table IX), **and** ☐ Reduction in HbA_{1c} < 1% required in order to reach patient-specific goal.
At Step 2: Add-on therapy as part of an oral two-drug regimen (must meet all criteria) ☐ Inadequate glycaemic control on monotherapy with metformin (at maximally tolerated dose) or a sulphonylurea (at least at half of maximal dose or highest tolerated dose), **and** ☐ Unable to tolerate or has contraindications to addition of the second, as yet unused agent, from the above mentioned (metformin or sulphonylurea), **and** ☐ Reduction in HbA_{1c} < 1% required in order to reach patient-specific goal.
At Step 1: Use as monotherapy (must meet all criteria) ☐ Candidate for oral therapy and is intolerant of or has contraindications to use of both metformin and sulphonylureas, **and** ☐ Reduction in HbA_{1c} < 1% required in order to reach patient-specific goal.
Dose:
Refer to product labeling for dosing information.
Discontinuation:
Discontinue if HbA_{1c} reduction < 0.5% after three to six months of therapy.

9.5 GLP-1 agonists

9.5.1 Mechanism of action

Refer to the section on "the incretin effect" above.

9.5.2 Efficacy

The GLP-1 agonists are associated with a reduction in HbA_{1c} that is similar to introducing another oral agent or insulin (Table VI). Liraglutide appears to be slightly more potent than exenatide, especially where fasting glucose is concerned. This effect results from the longer activity profile of liruglutide. The main advantage is that unlike most other diabetes drugs, the GLP-1 agonists promote weight loss. In the LEAD-6 study which compared liraglutide 1.8mg with exenatide 10 µg twice daily in patients inadequately controlled on metformin and / or a sulphonylurea, the mean weight loss over 26 weeks was about 3kg. The HbA1C reduction with liraglutide was 1.1% versus 0.8% with exenatide.

9.5.3 Dosing

Exenatide and liraglutide are examples of GLP-1 agonists. The GLP-1 agonists are available only as injectables in the form of pen devices. Exenatide is distributed as 5 µg and 10 µg pens; liraglutide, as a single multi-dose pen delivering 0.6–1.8 mg per injection. The dose of liraglutide should not exceed 1.2 mg, as the 1.8 mg is only marginally more effective.

The GLP-1 agonists are approved for combination therapy with metformin and/or sulphonylureas. Liraglutide is also licensed for use as initial monotherapy. There are some promising data on combinations with insulin, but this is not yet an approved indication. There is no data on combinations with acarbose or DPP-4 inhibitors.

Table VII provides a summary of the dosing information of the GLP-1 agonists.

9.5.4 Adverse effects and contraindications

While the GLP-1 agonists do not, by themselves, cause hypoglycaemia, the risk is increased when used with sulphonylureas. It is advisable to reduce the sulphonylurea dose when adding a GLP-1 agonist.

The common side-effect on initiating therapy is nausea and vomiting (approximately 25%), and this can be severe, leading to discontinuation in some. It is usually transient (4-8 weeks), can be minimised by titrating up the dose slowly, and it responds to anti-nausea medication. Both the GLP-1 agonists should probably be avoided in patients with significant gastrointestinal disease, particularly gastroparesis.

Recently, reports of pancreatitis with GLP-1 agonists have emerged. It is not clear whether pancreatitis is directly related to therapy but these drugs are best avoided in patients with a history of or potential for pancreatic disorders. Patients should be warned to report symptoms suggestive of pancreatitis immediately, discontinue the drug immediately on suspicion and not to restart a GLP-1 agonist if the diagnosis of pancreatitis is confirmed.

In animal models, liraglutide was associated with the development of C cell tumours. The possible effect on medullary thyroid carcinoma (MTC) in humans is not known. Nevertheless, liraglutide is contraindicated in

Table VI: Mean expected reduction in HbA1c levels for the GLP-1 agonists

	Exenatide	Liraglutide 1.2mg
Monotherapy	0.9%	1.1%
Added to existing metformin	Up to 1.4%; mean 1.0%	1.0%
Added to existing sulphonylurea	Up to 1.4%; mean 1.0%	1.1%
Added to existing metformin plus a sulphonylurea	1.1%	1.3%

Table VII: Dosing information of GLP-1 agonists

	Exenatide	Liraglutide
Recommended daily dose	Initial dose: 5 µg per dose, twice daily. If initial dose is tolerated and a dosage increase is indicated, increase the dose to 10 µg twice daily after one month of therapy.	Initial dose: 0.6 mg per day for one week. After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycaemic control, the dose can be increased to 1.8 mg.
Dosing frequency	Twice daily, any time within the 60-minute period before the morning and evening meals. Should not be administered after a meal. If a dose is missed, the treatment regimen should be resumed with the next scheduled dose.	Once daily, any time of day, independently of meals
Renal impairment	Contraindicated if eGFR < 30 ml/minute	No adjustment
Use with sulphonylureas	A lower dose of the sulphonylurea may be required, as hypoglycaemia has been reported more often in those treated with this combination	
Injection sites	Thighs, abdomen or upper arms	

Table VIII: GLP-1 agonists in the 2012 SEMDSA treatment algorithm

Contraindications
- There is a compelling indication for insulin therapy. - History of hypersensitivity to GLP-1 agonists. - Renal failure (consult product label to assess suitability). - Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (liraglutide). - Patient has severe gastrointestinal disease, including gastroparesis. - Patient has a history of pancreatitis. - Relative exclusions to use include triglyceride level > 10 mmol/l, gallstones with intact gallbladder, and alcohol abuse. - Planned treatment regimen includes a DPP-4 inhibitor, meglitinide or acarbose (unstudied). - Patient is not obese
Indications for GLP-1 agonist use
At Step 3: Add-on therapy as part of a three-drug regimen (must meet all criteria) ☐ Inadequate glycaemic control on combination therapy with maximally tolerated doses of metformin and sulphonylureas, **and** ☐ Patient is not a candidate for a third oral agent from step 3, **and** ☐ Patient is a poor candidate for insulin therapy (see Table IX), **and** ☐ Reduction in HbA_{1c} < 1,5% required in order to reach patient-specific goal.
At Step 2: Add-on therapy as part of a two-drug regimen (must meet all criteria) ☐ Patient has not achieved desired HbA_{1c} with one oral agent and is not a candidate for any other agent (oral or insulin) available at Step 2; **and** ☐ Reduction in HbA_{1c} < 1.5% required in order to reach patient-specific goal.
Dose
Refer to product labeling for dosing information.
Follow-up
Only continue therapy beyond six months if there has been a good clinical response to therapy: - HbA_{1c} reduction > 0.5% *and* weight loss > 3%, *or* - HbA_{1c} reduction > 1%, *or* - Weight loss > 5%

patients with a history of MTC or multiple endocrine neoplasia syndrome (MENS) type 2.

Exenatide is cleared by the kidneys, and should not be prescribed in patients with severe renal impairment (i.e. eGFR < 30 ml/minute).

9.5.5 GLP-1 agonists in the 2012 SEMDSA treatment algorithm

The clinical use of GLP-1 agonists is summarised in Table VIII .

Table IX: Circumstances where insulin therapy may not be desirable

- Insulin allergy
- Failure or inability to master injections or self-titration
- Frequent or severe hypoglycemia despite multiple dosage adjustments
- Circumstances exist where the risk of severe hypoglycemia and/or its potential consequences are significant and/or catastrophic
- Workers with frequent rotating shifts
- Occupations such as truck or bus drivers / heavy machinery operators)
- Obesity related morbidity which has worsened or is likely to worsen significantly with weight gain from insulin therapy

9.6 Thiazolidinediones

Thiazolidinediones are drugs that act as selective ligands for the nuclear transcription factor, peroxisome proliferator-activating receptor gamma (PPARγ), and cause increased insulin sensitivity through multiple mechanisms. These mechanisms include alteration in fatty acid uptake and in adipokine release. Rosiglitazone and pioglitazone belong to this class. These drugs are licensed for the treatment of type 2 diabetes, either alone or in combination with metformin, sulphonylureas and insulin.

Both rosiglitazone and pioglitazone have a modest effect on glycaemic control and, in maximal doses, lower HbA_{1c} by 1-1.5%. Both drugs increase high-density lipoprotein (HDL) cholesterol by approximately 10%. Pioglitazone has a neural effect on low-density lipoprotein (LDL) cholesterol, whereas rosiglitazone increases LDL cholesterol. Variable effects on triglycerides have been reported, and both agents lower blood pressure. Approximately 1-2 kg of weight gain occurs for every 1% reduction in HbA_{1c}.

In A Diabetes Outcome Progression Trial (ADOPT), rosiglitazone demonstrated superior durability in glycaemic control when compared to glibenclamide and metformin. A greater improvement in insulin sensitivity and beta cell function was also noted with rosiglitazone. Rosiglitazone has, however, been associated with an increase in adverse cardiovascular events in a meta-analysis, with and odds ratio for myocardial infarction of 1.43 [95% confidence interval (CI) 1.03-1.98, p=0.03]. A more recent meta-analysis has confirmed these initial findings. The Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Combination Therapy for Type 2

Diabetes (RECORD) trial showed an increased risk of heart failure and bone fractures when rosiglitazone was added to metformin or sulphonylurea drugs, but no increase in cardiovascular morbidity or mortality.

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) was a secondary prevention study in subjects with type 2 diabetes and pre-existing cardiovascular disease. The addition of pioglitazone 45 mg daily to conventional therapy was inconclusive for the composite primary end-point, but led to a 16% reduction in a composite secondary end-point of death, non-fatal myocardial infarction and stroke (hazard ratio 0.841, 95% CI 0.72-0.98, p=0.0273) when compared to placebo. The Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial showed a reduction in progression of carotid intima media thickness with pioglitazone a compared to glimepiride, and the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial showed a more favourable effect of pioglitazone on coronary atheroma volume, measured with intracoronary ultrasound, as compared to glimepiride.

Both rosiglitazone and pioglitazone cause fluid retention, and may precipitate or exacerbate cardiac failure. Heart failure approximately doubled in the rosiglitazone group in the RECORD trial, when compared to an active control. In the PROactive study, 11% of subjects in the pioglitazone group developed heart failure, compared to 8% in the control group (p<0.0001), although there was no increase in the rate of deaths as a result heart failure.

Fractures have occurred with greater frequency in association with both rosiglitazone and pioglitazone. In the ADOPT study, upper limb and foot fractures occurred significantly more frequently in women (but not men) treated with rosiglitazone, when compared to those treated with either metformin or glibenclamide. In the PERISCOPE trial, fractures occurred in 3% of the group treated with pioglitazone, as opposed to none in the control group, p=0.004.

Concern has been raised regarding a possible increase in neoplasms associated with the use of thiazolidinediones. In the RECORD trial, there was no increase in the incidence of malignancy in the rosiglitazone group. In the PROactive study, more bladder cancers and fewer breast cancers were reported in the pioglitazone group, although the small numbers prevented conclusions from being made. More recently, an interim report of a large managed health organisation study showed an excess of bladder cancers in subjects treated with pioglitazone for longer than 24 months (hazard ratio 1.4, 95% CI 1.03-2.00), but not for those exposed to shorter duration therapy. No increased risk of 10 other common cancers was found in a parallel study. In view of the possibility of an increased risk of bladder cancer, the French medicine regulatory agency (AFSSAPS) suspended the use of pioglitazone in that country in June 2011. In July 2011, the manufacturer of rosiglitazone (GlaxoSmithKline) voluntarily discontinued the supply of rosiglitazone (Avandia) in South Africa.

9.6.1 Thiazolidinediones in the 2012 SEMDSA treatment algorithm

Pioglitazone has been removed from the 2012 treatment algorithm. Rosiglitazone is no longer available in South Africa.

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10. Glucose control: Insulin-based therapies

Patients with type 2 diabetes mellitus often require insulin to achieve glycaemic control. However, the variable data on a wide array of insulins, coupled with active marketing from pharmaceutical companies, often makes the initial choice of insulin and regimen confusing. In this section, we attempt to briefly summarise the data on the use of various insulins and regimens in patients with type 2 diabetes, and provide recommendations for the initiation of insulin in these patients.

JEMDSA 2012;17(2):S32-S35

10.1 Clinical trial evidence to guide the rational use of insulin in the treatment of type 2 diabetes

Most studies assessing the use of insulin in patients with type 2 diabetes mellitus (diabetes) are short-term, pharmaceutical company-sponsored trials that do not provide robust evidence. However, there are a few studies and meta-analyses that can be used to guide the rational use of insulin in the treatment of type 2 diabetes.

10.1.1 United Kingdom Prevention of Diabetes Complications Study (UKPDS)

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 or insulin had relative reductions in risk. These risk reductions persisted at 10 years for 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.[1]

10.1.2 Treating To Target in Type 2 Diabetes (4-T study)

The 4-T study showed that, in patients with type 2 diabetes randomly assigned to receive a basal, biphasic or prandial insulin regimen, the mean glycated haemoglobin (HbA_{1c}) levels at one year were similar in the biphasic (7.3%) and prandial groups (7.2%, P=0.08), but higher in the basal group (7.6%, P < 0.001) for both comparisons).[2] However, this slightly superior reduction in HbA_{1c} was accompanied by a higher number of hypoglycaemic events per patient per year (biphasic = 5.7, prandial = 12.0, basal = 2.3; P < 0.001), and higher respective mean weight gain (biphasic 4.7 kg, prandial 5.7 kg, basal 1.9 kg; P < 0.001) in the basic and prandial groups. Rates of adverse events were similar across the three groups.

10.1.3 4-T study: three-year follow-up

The three-year follow-up of the 4-T study showed that median HbA_{1c} levels were similar for patients receiving biphasic (7.1%), prandial (6.8%), and basal (6.9%) insulin-based regimens (P = 0.28). But, the median rates of hypoglycaemia per patient per year were lowest in the basal group (1.7), higher in the biphasic group (3.0), and highest in the prandial group (5.7) (P < 0.001 for the overall comparison).[3] 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.

10.1.4 Siebenhofer et al

Siebenhofer et al conducted a meta-analysis to assess the effects of short-acting insulin analogues versus regular human insulin.[4] They included randomised controlled trials with an intervention duration of at least four weeks, and identified 49 randomised, controlled trials (n = 8 274) that met their inclusion criteria. However, most studies were of poor methodological quality. In patients with type 2 diabetes, the weighted mean difference (WMD) of HbA_{1c} was 0.0% [95% confidence interval (CI): -0.1 to 0.0]. The WMD of the overall mean hypoglycaemic episodes per patient per month was -0.2 (95% CI: -0.5 to 0.1) for analogues, in comparison to regular insulin in patients with type 2 diabetes. For studies in patients with type 2 diabetes, the incidence of severe hypoglycaemia ranged from 0-30.3 (median 0.3) episodes per 100 person-years for insulin analogues, and from 0-50.4 (median 1.4) for regular insulin. No study was designed to investigate the possible long-term effects (e.g. mortality and diabetic complications) of each insulin, in particular in patients with diabetes-related complications.

10.1.5 Horvath et al

Horvath et al conducted a systematic review to assess the effects of long-term treatment with long-acting insulin analogues (insulin glargine and insulin detemir) compared to neutral protamine Hagedorn (NPH) insulin in adult patients with type 2 diabetes.[5] They included randomised, controlled trials that had a duration of at least 24 weeks. Six studies compared insulin glargine to NPH insulin, and two studies compared insulin detemir to NPH insulin. In total, 1 715 patients were randomised to insulin glargine and 578 patients to insulin detemir, and the duration of the trials ranged from 24-52 weeks. There were no significant differences in reduction in HbA_{1c} and adverse effects, but there was a significant difference in the rate of symptomatic, overall and nocturnal hypoglycaemia, with the results favouring analogue insulin over NPH. There were no statistically significant differences in severe hypoglycaemia rates. In addition, long-acting analogues had no beneficial effect on patient-oriented outcomes like mortality, morbidity, quality of life or costs.

10.1.6 Monami et al

Monami et al conducted a meta-analysis to assess the differences, with respect to HbA_{1c}, incidence of hypoglycaemia and weight gain, between NPH human insulin and the long-acting analogues deternir and glargine in patients with type 2 diabetes.[6] They included all randomised, controlled trials with a duration of longer than 12 weeks, and 14 were identified that met their inclusion criteria. The analysis did not show a significant improvement in HbA_{1c} when comparing the long-acting analogues with NPH human insulin. However, when analysed separately, NPH showed significant superiority (by 0.1%) over detemir, but not over glargine. Detemir, and not glargine, was associated with a significantly smaller weight gain than NPH human insulin. Both analogues were associated with a reduced risk of nocturnal and symptomatic hypoglycaemia [odds ratios (OR) 0.46 (0.38-0.55) and 0.69 (0.60-0.800; all P <0.01).

10.1.7 Singh et al

Singh et al conducted a meta-analysis of the published literature to determine the efficacy and safety of insulin analogues for the management of diabetes.[7] They included 68 randomised, controlled trials in the analysis of rapid-acting insulin analogues, and 49 in the analysis of long-acting insulin analogues. For reduction in HbA_{1c}, they found minimal differences between rapid-acting insulin analogues and regular human insulin in adults with type 1 diabetes (WMD for insulin lispro –0.09%, 95% CI –0.16% to –0.02%; WMD for insulin aspart –0.13%, 95% CI –0.20% to –0.07%). Similar outcomes were observed among patients with type 2 diabetes (WMD for insulin lispro –0.03%, 95% CI –0.12% to –0.06%; WMD for insulin aspart –0.09%, 95% CI –0.21% to 0.04%). There were marginal differences in reduction of HbA_{1c} between long-acting insulin analogues and NPH insulin among adults with type 1 diabetes (WMD for insulin glargine –0.11%, 95% CI –0.21% to –0.02%; WMD for insulin detemir –0.06%, 95% CI –0.13% to 0.02%), and among adults with type 2 diabetes (WMD for insulin glargine –0.05%, 95% CI –0.13% to 0.04%; WMD for insulin detemir 0.13%, 95% CI 0.03% to 0.22%). There were inconsistent benefits in terms of reduced hypoglycAemia in the studies.

10.1.8 Manucci et al

Manucci et al conducted a meta-analysis to determine whether short-acting insulin analogues, in comparison with regular human insulin (HRI), provide better control of postprandial glucose and HbA_{1c}.[8] They included all randomised, controlled trials with a duration of longer than four weeks comparing short-acting insulin analogues (lispro, aspart or glulisine) with HRI in patients with type 2 diabetes. They identified 13 trials (seven with lispro, four with aspart and two with glulisine) that met their inclusion criteria. Short-acting analogues were found to reduce HbA_{1c} by 0.4% (0.1-0.6%; P = 0.027) in comparison with HRI. There was a significant improvement in self-monitored two-hour postprandial blood glucose. There was no significant difference in the overall rate of severe hypoglycaemia with short-acting analogues and HRI [Mantel-Haenszel OR for 95% CI 0.61 (0.25-1.45)].

10.2 Insulin preparations

The insulin prepaprations currently available in South Africa are summarised in Table I. Brand names are included for clarity and ease of reference. Note that onset and peak insulin action can vary considerably depending on injection site.

10.3 Insulin therapy in the 2012 SEMDSA treatment algorithm

10.3.1 At Step 1

Consider insulin as first-line therapy in the setting of severely uncontrolled diabetes with any of the following features:

- Catabolism (marked weight loss)
- Fasting plasma glucose levels > 14 mmol/l
- Random glucose levels consistently > 16.7 mmol/l
- HbA_{1c} > 10%
- Ketonuria or ketocidosis.

Use either pre-mixed insulin twice daily or basal-bolus intensive insulin therapy (specialist referral recommended).

10.3.2 At Step 2 or 3

Add insulin to other therapies, as second- or third-line therapy, when individualised glycaemic targets are unmet. Add either basal or pre-mixed insulin, as detailed below.

Table I: Insulin preparations and pharmacokinetics

Type	Onset	Peak	Duration
Rapid-acting analogues Aspart (NovoRapid®) Glulisine (Apidra®) Lispro (Humalog®)	5-15 minutes	30-90 minutes	3.5-4.5 hours
Short-acting regular Actrapid®, Humulin-R®, generic	30-60 minutes	2-3 hours	5-8 hours
Intermediate-acting NPH (neutral protamine Hagedorn) (Humulin-N®, Protaphane®, generic)	2-4 hours	4-10 hours	10-18 hours
Long-acting basal analogues Detemir (Levemir®) Glargine (Lantus®)	2-4 hours	No peak	Up to 24 hours
Pre-mixed human (biphasic) Regular + NPH (Actraphane®, Humulin 30/70®, Insuman®, generic)	30-60 minutes	Dual peak	10-18 hours
Pre-mixed analogues (biphasic) Pre-mixed aspart (NovoMix®) Premixed lispro (Humalog Mix25®, Humalog Mix50®)	5-15 minutes	Dual peak	10-16 hours

10.3.2.1 Basal insulin

1. Maintain the patient on all oral medications.
2. Start with 8 units of intermediate- or long-acting insulin at 21h00-22h00 (bedtime).
3. The patient must monitor fasting (on waking) fingerprick glucose daily, and calculate the average fasting glucose every 3 to 7 days. The target glucose will vary, depending on the individualised target HbA_{1c}. (See the section on glycaemic targets.)
4. Titrate the insulin dose by 2 units every three to seven days, until the fasting glucose is within the target range.
5. If unexplained nocturnal hypoglycaemia occurs, instruct the patient to reduce the basal insulin dose by 10% and to stop titration until the next visit. Consider a long-acting insulin analogue in this situation (if not already in use).
6. Consider using a long-acting insulin analogue (glargine or 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 hypoglycemia and/or its potential consequences can be significant and/or catastrophic (e.g. workers with frequent rotating shifts and occupations such as truck or bus drivers or heavy machinery operators).

10.3.2.2 Pre-mixed insulin

1. Stop all oral antidiabetic drugs, except metformin.
2. The patient must be seen by a diabetes nurse educator and to be instructed on injection technique, fingerprick-glucose monitoring, and hypoglycaemia and hyperglycemia management.
3. Calculate the starting total daily insulin dose using the following formula:

   Total number of units of insulin per day
   = 0.3 x body weight (kg)

   (An alternative is to start with 10 units twice a day before meals.)
4. Start by giving two thirds of the dose before breakfast and one third of the dose before supper.
5. 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}. (See the section on glycaemic targets.)
6. Titrate the pre-breakfast insulin dose to achieve the pre-supper target glucose level, and vice versa. Titration increments can be calculated from a standard insulin sliding scale. 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 hypoglcaemic event) by 10% and to

stop titration until the next visit. Consider analogue insulins in this situation (if not already in use).

10.3.3 General notes

- All patients must be seen by a diabetes educator to be instructed on injection technique, fingerprick-glucose monitoring and hypoglycaemia and hyperglycaemia management.
- Insulin pen devices are preferred delivery devices and should be funded. The smallest effective needle size should be prescribed (range 29 to 32 gauge and 4 mm to 12.7 mm in length).
- Patients must be counselled on sharps disposal, and to use a pharmacy or clinic for disposal.
- The abdomen, thighs or arms are recommended injection sites.
- The insulin regimen must be matched with the patient's lifestyle, acceptance and numeracy skills. It is not appropriate to initiate basal-bolus insulin therapy in a 75-year-old who cannot self-monitor or titrate insulin doses.
- All patients should be give written instructions for titration.
- Titration must be ongoing.
- Re-evaluate the current regimen if targets are not reached within three to six months.
- If glycaemic targets are not met with basal or biphasic insulin, intensive insulin therapy (with multiple daily injections) must be considered.
- All patients experiencing a severe hypoglycaemic episode must be instructed to stop titration and see their healthcare provider immediately.
- Specialist referral is appropriate at any stage if glycaemic targets remain unmet.

10.4 Additional insulin requirements during periods of illness or stress

During periods of illness and stress, or when the blood glucose level is uncontrolled for any reason, patients may require additional insulin, or escalation of therapy to include insulin therapy.

Additional insulin, with appropriate instructions for administration, should only be given to patients who are able to test their glucose at home, and who will be able to carry out the instructions safely and correctly when their blood glucose is raised.

Only short-acting insulin should be used, and it should be added to the usual insulin doses and injected before each meal. This can be added to the usual insulin regimen in one of two ways:

1. Increase the dose of the short-acting insulin by 10% of the total daily insulin dose; or
2. Increase the usual short-acting dose by 20%.

The usual insulin doses should not be discontinued, and oral agents should also still be taken. If the patient is vomiting or dehydrated, however, metformin should be discontinued until medical advice is sought.

If unable to reduce the blood glucose levels and bring about a resolution of the hyperglycaemia, patients should be advised to contact their doctors or go to the clinic or hospital urgently. If the blood glucose level remains > 15 mmol/l, despite two corrective doses of insulin, or if the patient is not on insulin and the blood glucose remains > 15 mmol/l over a four-hour period, medical review is required.

The patient's diet should not be adjusted. If this is not possible, small, frequent helpings of soft foods or liquids containing carbohydrates should be taken (e.g. porridge, soup).

Plenty of fluids (e.g. water, diet mineral drinks) should be ingested. If the patient is feeling nauseous and not tolerating solids, he or she should drink unsweetened drinks. Small quantities of sweetened drinks (e.g. fruit juice) should also be included to prevent hypoglycaemia.

If the patient is vomiting, or if consciousness is impaired, assistance should be sought from a doctor or clinic or hospital urgently.

The urine of patients who require additional insulin should be checked for ketone. This also applies to patients with type 1 diabetes. If the ketones are strongly positive and the blood glucose is > 22 mmol/l, the doctor or hospital or clinic should be contacted urgently.

The blood glucose should be checked before every meal, and at bedtime

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11. The 2012 SEMDSA Treatment Algorithm for Type 2 Diabetes

Metformin remains the drug of first choice in type 2 diabetes, based on its availability, tolerability and efficacy, particulary in overweight type 2 diabetes patients. Despite a long list of potential contraindications, it is remarkably well tolerated. Metformin therapy should be maintained, even when other classes of drugs are added, provided there are no contraindications.

Sulphonylurea drugs have formed an integral part of the management of type 2 diabetes mellitus for many years, and a number of studies have demonstrated the efficacy of this class of drug in glucose control. The major adverse effect is hypoglycaemia, and this has been demonstrated to be more frequent and severe with glibenclamide. The use of this drug is therefore discouraged.

Acarbose is a safe nonsystemic drug that is weight neutral and does not cause hypoglycaemia. It has never been a popular choice because of its gastrointestinal adverse effects. However, the need to intensify therapy early, together with the cardiovascular and mortality risks associated with hypoglycaemia, makes this agent a useful choice in some circumstances.

The newer incretin-based therapies are an attractive therapeutic option, also without the burden of weight gain and hypoglycaemia. However, they are relatively new with no long-term outcomes data, and should be reserved as alternative therapies when the older conventional therapies are not suitable.

Thaizolidinediones have been removed from the current guidelines, in view of the withdrawal of rosiglitazone from the market and the reported bladder toxicity of pioglitazone.

Insulin therapy remains an option at all stages of management.

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Internationally, there are a number of guidelines advising on the pharmacological management of type 2 diabetes mellitus (diabetes). However, none of these were considered suitable by the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) to adopt without modification.

In formulating the current guideline, the Guideline Committee considered the following challenges:

- Type 2 diabetes is a poorly managed disease, with fewer than 50% of patients achieving glycaemic targets, even in some of the most advanced centres in the world. This figure is likely to be much lower in the primary-care settings of South Africa.
- Type 2 diabetes is not a homogenous disease. It is prevalent across all socio-economic strata, all ethnic groups, all age groups (after puberty), and all categories of body mass index/abdominal circumference, and in individuals with a highly variable genetic background, food intake and level of physical activity.
- Therefore, the exact pathogenesis of the disease is likely to be highly variable, and patients will manifest varying degrees of a primary and/or secondary insulin secretory defect and/or insulin resistance at the time of contact with the healthcare provider. Each individual will display even further variability, depending on the duration and stage of the disease. Thus, each individual patient with type 2 diabetes is unique, and it is important to appreciate the potential underlying mechanisms resulting in hyperglycaemia at every stage of the disease.
- The great diversity found in patients with type 2 diabetes makes it unlikely that a rigidly uniform therapeutic approach, with a limited number of drugs, will find widespread acceptance and be successful in treating this disorder. Thus, while a simple treatment algorithm is desirable, approaches utilising

limited therapeutic options can also have limited success and adherence (both amongst healthcare practitioners and patients). The Guideline Committee has, therefore, sought to match the therapeutic options with the diverse clinical profiles encountered in our patients, while still offering a systematic and logical approach to drug management.

- The majority of patients with type 2 diabetes are treated at primary-care level (public and private sector), and the current system of care is inadequate. In the absence of health systems reforms, it is only through alteration of the current therapeutic strategies that any significant impact will be made on the quality of diabetes care in South Africa. It is beyond the scope of this guideline to advise on reform in the healthcare system. However, the guideline does have the potential to improve glycaemic control if, by following these recommendations, the prescribing habits of healthcare providers and patients' adherence to therapies are improved.
- The Guideline Committee attempted to facilitate safe prescribing at primary-care level (by doctors and nurse practitioners) by including agents that are relatively innocuous early in the course of the disease [e.g. metformin, acarbose and dipeptidyl peptidase-4 (DPP-4) inhibitors]. It is hoped that the greater availability of agents that do not cause weight gain or hypoglycaemia will improve adherence to glycaemic targets (prescribers can escalate therapy quickly and safely), improve patient compliance with medications, reduce the need for home-glucose monitoring, and limit the number of patients needing referral to secondary- and tertiary-care levels.
- The Guideline Committee considered the good evidence from clinical and bariatric surgical trials which indicate that caloric restriction can result in significant improvements in measures of insulin resistance and pancreatic beta-cell function. In the context of the obesity pandemic and its almost certain role in the causality of a significant proportion of type 2 diabetes, it was felt that therapies which have the potential to restrict caloric intake, cause weight loss or minimise weight gain had to be included in the algorithm at all levels of care.

Subsequent to the development of this SEMDSA algorithm in September 2011, the International Diabetes Federation (IDF) released the "IDF Treatment Algorithm for People with Type 2 Diabetes" in December 2011 at the World Diabetes Congress in Dubai, and published it on their website (http://www.idf.org/treatment-algorithm-people-type-2-diabetes cited 18 March 2012). This IDF algorithm is not dissimilar to the SEMDSA algorithm, save for the decision by SEMDSA to exclude the thiazolidenediones.

General considerations when using the algorithm:

It needs to be emphasised that pharmacological therapy should always be accompanied by ongoing lifestyle modification.

Patients must be informed from diagnosis that a progressive increase in the dose and number of medications is the rule, given the natural history of type 2 diabetes, and that insulin therapy will almost invariably be required eventually. However, overweight and obese patients should also be informed that normalisation of body weight has the potential to dramatically improve insulin resistance and secretion, and to possibly cause long-term remission of type 2 diabetes.

The aim of therapy is to achieve and maintain the glycated haemoglobin (HbA_{1c}) below the patient's individualised target level. HbA_{1c} above this target must serve as a call to action on the part of the practitioner; medication must be increased and lifestyle measures intensified, except if the risk of hypoglycaemia is unacceptable.

The preferred therapies for type 2 diabetes were chosen on the basis of proven micro- and or macrovascular benefits (as primary endpoints) in randomised, controlled clinical trials. These therapies include metformin, glibenclamide, gliclazide modified-release, and human insulins. The reasons for not recommending glibenclamide are discussed in the section entitled "Glycaemic control: non-insulin therapies".

The algorithm should be read in conjunction with Table II (Antihyperglycaemic therapies used in type 2 diabetes), which is a summary of each drug class, as well as the previous sections on glucose control with non-insulin and insulin-based therapies, which discuss each drug class in more detail, as well as how they fit into the algorithm. Referral to an endocrinologist is appropriate at any stage if glycaemic targets are not met.

Table I: 2012 SEMDSA treatment algorithm for type 2 diabetes

2012 SEMDSA treatment algorithm for type 2 diabetes

SEMDSA Society for Endocrinology, Metabolism and Diabetes of South Africa

Use this algorithm only if the patient does not have features of severe decompensation.[a]
Progress down this algorithm within three months if HbA_{1c} remains > 7% (or above the individualised target).
Choose therapies that are likely to produce the HbA_{1c} reduction required to achieve the target.[b]
Do not proceed with drug therapy without annual serum eGFR measurement

Lifestyle measures plus	Preferred therapies		Alternative therapies for special circumstances[c]		
STEP 1: INITIATE AT LEAST ONE ORAL DRUG AT DIAGNOSIS	Metformin		SU	DPP-4i	Acarbose
↓					
STEP 2: COMBINE ANY TWO DRUGS[d]	Metformin	SU[e]	Incretin	Acarbose	Basal insulin
↓					
STEP 3: COMBINE THREE DRUGS	Metformin + SU + basal Insulin (or metformin + pre-mix insulin)		Metformin + SU + Incretin	Metformin + SU + acarbose	
↓					
STEP 4: MORE ADVANCED THERAPIES	Refer to specialist for basal + mealtime insulin ± metformin ± acarbose ± incretin		Metformin + pre-mix insulin (if not used yet)		

DPP-4i: dipeptidyl peptidase-4 inhibitors; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; HbA_{1c}: glycated haemoglobin; SU: sulphonylurea (not glibenclamide)
a: Severe decompensation includes any of FPG > 15 mmol/l, HbA_{1c} > 11%, marked polyuria and polydipsia, weight loss > 5% or ketoacidosis. Refer the patient for specialist care (Step 4).
b: Refer to Table I for expected HbA_{1C} reductions.
c: Refer to text in Section 9.
d: If, at diagnosis, the patient's HbA_{1c} is >9% without features of severe decompensation, consider initiating therapy at Step 2.
e: A meglitinide may replace the sulphonylurea in patients with normal fasting glucose but elevated post-prandial glucose and HbA_{1c}.

Table II: Antihyperglycaemic agents used in type 2 diabetes

Class	Drug (brand name)	Effect on HbA1c[a]	Therapeutic considerations	Disadvantages
Alpha glucosidase inhibitors	Acarbose (Glucobay®)	↓	Negligible hypoglycaemia risk as monotherapy Nonsystemic effect Weight neutral Targets postprandial hyperglycaemia	Gastrointestinal effects (flatulence, diarrhoea) Frequent dosing (mealtimes)
Biguanide	Metformin (Glucophage®, Glucophage XR®)	↓↓	Negligible hypoglycaemia risk, as monotherapy Weight neutral as monotherapy, promotes less weight gain when combined with other antihyperglycaemic agents, including insulin Proven reduction in cardiovascular events and mortality in obese subjects Metformin extended-release formulation has better gastrointestinal tolerability and, in the event of metformin intolerance, is preferred to switching to another class of drug	Frequent gastrointestinal side-effects (diarrhoea, abdominal cramping); 5-10% discontinuation Lactic acidosis (rare) Vitamin B_{12} deficiency appears to be more common than initially appreciated Renal impairment: reduce dose to 1 000 mg/day if estimated glomerular filtration rate (eGFR) < 45ml/minute/1.73m^2, and discontinue if eGFR < 30 ml/minute/1.73m^2
Incretins	*Dipeptidyl peptidase-4 (DPP-4) inhibitors:* Linagliptin[b] Saxagliptin (Onglyza®) Sitagliptin[b] Vildagliptin (Galvus®)	↓	Negligible hypoglycaemia risk as monotherapy Weight neutral Improves postprandial control Drug-specific recommendations for hepatic and renal disease	Occasional reports of urticaria and angioedema Cases of pancreatitis observed Newer agents with unknown long-term safety
	Glucagon-like peptide (GLP-1) agonists: Exenatide (Byetta®) Liraglutide (Victoza®)	↓↓	Negligible hypoglycaemia risk as monotherapy Enhances satiety and causes weight loss Possible potential for improved beta-cell mass and function. Avoid initiating therapy in individuals in whom the potential for dehydration poses a considerable risk (e.g. frail elderly, multiple co-morbid conditions)	Injectable Initial gastrointestinal side-effects (nausea, vomiting, diarrhoea) Cases of acute pancreatitis observed Liraglutide causes C-cell hyperplasia and medullary thyroid tumours in animals Newer agents with unknown long-term safety
Insulin secretagogues	*Sulphonylureas*[c] Glibenclamide (Daonil®, Euglucon®, generic) Gliclazide (Diamicron®, Diamicron MR, generic) Glimepiride (Amaryl®, generic) Glipizide (Minidiab®)	↓↓	Generally well tolerated Proven reduction in microvascular endpoints (UKPDS[d] and ADVANCE[e] studies); reduction in cardiovascular events and mortality in the long term (UKPDS post-trial monitoring). Relatively rapid glucose-lowering response; useful in the patient with symptomatic hyperglycaemia. Consider using other classes of antihyperglycemic agents in patients at high risk of hypoglycaemia (e.g. the elderly, renal and hepatic failure). If a sulphonylurea must be used in such individuals, gliclazide modified-release is associated with the lowest incidence of hypoglycaemia. Glimepiride and glipizide are associated with less hypoglycaemia than glibenclamide.	Hypoglycaemia relatively common, but variable. Can cause severe hypoglycaemia, including episodes necessitating hospital admission and causing death (particularly glibenclamide, and particularly when renal function is impaired) Causes weight gain (2-5 kg); worst with glibenclamide May blunt myocardial ischaemic preconditioning (particularly glibenclamide) Renal impairment: glibenclamide contraindicated if eGFR < 60 ml/minute/1.73m^2; glimepiride and glipizide dose may need to be reduced
	Meglitinides Nateglinide (Starlix®) Repaglinide (NovoNorm®)	↓ ↓↓	Nateglinide is the least effective secretagogue Targets postprandial glycaemia; use if fasting glucose is at target, but HbA_{1c} remains high. Associated with less hypoglycaemia than the sulphonyureas in the context of missed meals; useful for patients with unpredictable mealtimes	Cause hypoglycaemia Cause weight gain May blunt myocardial ischaemic preconditioning Frequent dosing (at mealtimes)

Table II (cont.): Antihyperglycaemic agents used in type 2 diabetes

Class	Drug (brand name)	Effect on HbA1c[a]	Therapeutic considerations	Disadvantages
Insulin	*Rapid-acting analogues* Aspart (NovoRapid®) Glulisine (Apidra®) Lispro (Humalog®) *Short-acting regular* (Actrapid®, Humulin-R®, generic) *Intermediate-acting* Neutral protamine Hagedorn (NPH) (Humulin-N®, Protaphane®, generic) *Long-acting basal analogues* Detemir (Levemir®) Glargine (Lantus®) *Pre-mixed human* Regular plus NPH (Actraphane®, Humulin 30/70®, Insuman®, generic) *Pre-mixed analogue* Pre-mixed aspart (NovoMix®) Pre-mixed lispro (Humalog Mix25®, Humalog Mix50®)	Depends on regimen and dosing, but up to ↓↓↓	Potentially greatest HbA_{1C} reduction and no maximal dose Numerous formulations and delivery systems allow for regimen flexibility When initiating insulin, consider adding bedtime intermediate-acting insulin or long-acting insulin analogue to daytime oral antihyperglycemic agents (although other regimens can be used) Intensive insulin therapy (IIT) regimen recommended if above fails to attain glycaemic targets Pre-mix (biphasic) insulins are somewhat less effective but have wider patient acceptability and appeal	Significant risk of hypoglycaemia Hypoglycemia risk highest with regular and NPH insulin; use analogue insulin in this circumstance. Increased risk of weight gain relative to sulphonylureas and metformin. Injectable Oedema is usually transient, but can be severe Initial reports of malignancies with glargine are unverified

a: Reduction in HbA_{1c}:
↓ <1% reduction in HbA_{1c}
↓↓ 1-2% reduction in HbA_{1c}
↓↓↓ >2% reduction in HbA_{1c}
b: Not registered for use in South Africa at time of publication (March 2012)
c: Refers to second-generation sulphonylureas; chlorpropamide is a commercially available first-generation sulphonylurea that is no longer in clinical use.
d: UKPDS: United Kingdom Prospective Diabetes Study
e: ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation

Adapted with permission from Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada

12. Hypoglycaemia

Hypoglycaemia is the complication most feared by patients with diabetes mellitus. It is a common and serious result of insulin and insulin secretagogue (e.g. sulphonylurea) treatment. Hypoglycaemia may manifest during sleep.

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12.1 Definition

Hypoglycaemia in diabetes mellitus (diabetes) is recognised when the plasma glucose level falls to < 4.0 mmol/l. Symptoms may occur at higher values when glucose levels decrease rapidly. Low finger-prick blood glucose levels should be confirmed with laboratory measurements, but treatment should not be withheld while awaiting results.

12.2 Complications

Severe hypoglycaemia may cause permanent neurological damage or brain death, and may be responsible for sudden death (the "dead in bed syndrome") related to cardiac arrhythmia.

Recent trials of intensive glycaemic control have demonstrated a clear relationship between hypoglycaemia and the risk of cardiovascular mortality. The risk of cardiovascular death was increased by 1.4- to 3.7-fold in patients with a recent hypoglycaemic episode in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and Veterans Affairs Diabetes Trial (VADT). Hypoglycaemia has therefore emerged as an important cardiovascular risk factor, equal to or greater in magnitude than other conventional risk factors (e.g. hypertension, dyslipidaemia).

12.3 Possible causes of hypoglycaemia in the diabetic patient

- Increased exercise (common)
- Decreased food intake (common): Missed or late meals, or small meals.
- Inappropriate insulin or insulin secretagogue dose.
- Progressive renal failure, causing decreased insulin clearance
- Alcohol intake.

Table I. Symptoms and signs of hypoglycaemia

Symptoms	Signs
- Hunger - Sweating - Palpitations - Tremor - Tingling sensation - Anxiety - Weakness - Faintness - Headache	- Change in behaviour - Confusion - Seizures - Coma

12.4 Presenting features

Table I provides a summary of the symptoms and signs associated with hypoglycaemia.

12.5 Treatment

12.5.1 Mild hypoglycaemia

Patients who are aware of the symptoms and signs of hypoglycaemia will be able to relieve the condition early by taking glucose or two to four teaspoons of sugar with a little water. If necessary, this step should be repeated within 10-15 minutes. Thereafter, slowly digestible carbohydrates (e.g. bread) and protein (e.g. milk) should be taken for prolonged restoration of the blood glucose.

Glucose or sucrose should always be carried by patients in their pockets or handbags, for emergencies.

12.5.2 Severe hypoglycaemia

Severe hypoglycaemia is defined as an event requiring the intervention of another person for relief of the 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 < 50 ml of 50% dextrose solution. Assess the clinical and biochemical response over the next 5-10 minutes.
3. 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 5% 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 sulphonylurea agents. For patients that are alcoholic or malnourished, continue the IV infusion with 5% dextrose in water plus thiamine 100 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 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 a normal or elevated blood glucose level, other causes of coma will need to be considered (e.g. meningitis). Urgent referral to hospital is indicated.
8. Refer all hypoglycaemic patients 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.

A glucagon emergency kit should be made available in emergency rooms. In addition, patients who experience recurrent severe hypoglycaemic reactions should be given one of these kits for home use; lay persons can be taught to safely administer glucagon using these kits.

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

12.6 Education

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

12.7 Recurrent hypoglycaemia

All patients with recurrent hypoglycaemia should be referred to hospital for assessment.

Consider the following in cases of recurrent hypoglycaemia:

- Inappropriate management
- Poor adherence to treatment
- Alcohol abuse
- Self-induced hypoglycaemia
- Advent of renal failure
- Hypoglycaemia awareness

12.8 Hypoglycaemia awareness

Recurrent hypoglycaemia may be the cause or consequence of hypoglycaemic unawareness. This complication occurs after some years of diabetes, and is associated with hypoglycaemia-associated autonomic failure. These patients do not exhibit the early symptoms of hypoglycaemia, and consequently present with neuroglycopenia (i.e. confusion, seizures, and coma). Evidence exists that, in some of these individuals, scrupulous avoidance of hypoglycaemia for several weeks can reverse hypoglycaemic unawareness.

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13. Hyperglycaemic emergencies

The hyperglycaemic emergencies, diabetic ketoacidosis and hyperglycaemic hyperosmolar state, should be suspected whenever patients have significant 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.

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13.1 The hyperglycaemic emergencies

13.1.1 Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is characterised by uncontrolled hyperglycaemia, 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.

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 most common precipitating factor in DKA and HHS is infection. Other precipitants include discontinuation of insulin, myocardial infarction and cerebrovascular accident. In elderly patients, restricted water intake due to the patient being bedridden can lead to dehydration and precipitate HHS. Drugs such as diuretics may exacerbate the condition. In addition, new-onset diabetes mellitus (diabetes) commonly leads to DKA in patients with type 1diabetes, and HHS in patients with type 2 diabetes mellitus. In a significant proportion of patients, no precipitant can be identified.

13.3 Clinical features

An acute DKA episode usually develops within 24 hours, whereas HHS usually evolves over several days to weeks. For both DKA and HHS, the classical clinical picture

Table I. Differentiation between the different types of hyperglycaemic coma

	Diabetic ketoacidosis	Hyperglycaemic hyperosmolar coma
History	Known type 1 diabete Newly diagnosed diabetes	Known type 2 diabetes Newly diagnosed diabetes
Precipitants	Infection Non-compliance on insulin	Infection Myocardial infarction Cerebrovascular accident Diuretic use
Age frequency	Younger patients	Usually older patients
Onset	Hours to days	Days to weeks
Symptoms	Polyuria Polydipsia Anorexia Nausea and vomiting Abdominal pain	Polyuria Polydipsia Increasing somnolence
Signs	Kussmaul respiration: Deep, sighing breathing Dehydration Confusion Nausea and vomiting	Severe dehydration Mental status changes Focal neurological signs 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

includes a history of polyuria, polydipsia, vomiting, dehydration, weight loss, weakness and change in mental status. The mental status can vary from mild confusion to profound lethargy or coma, and the latter is more common in HHS. Focal neurological signs and seizures may occur in HHS. Patients with DKA commonly complain of diffuse abdominal pain. Physical findings may include Kussmaul breathing in DKA only, or shock, with hypotension and tachycardia.

History taking and examination should not delay the initial investigations, management and referral to hospital. Rapid treatment is essential.

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

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

- Confirm the diagnosis. Check the capillary glucose and urine ketones to confirm hyperglycaemia and ketonuria.
- Administer intravenous (IV) fluids, beginning with normal saline. In a young patient with suspected DKA, infuse one litre of normal saline over the first hour. In an older patient with suspected HHS or cardiac compromise, change to 0.45 normal saline after the first litre of normal saline.
- Administer hourly boluses of 10 units of regular insulin IV, until the patient is transferred to hospital.
- Arrange immediate transfer to a hospital.

13.5 Management of hyperglycaemic emergencies in hospital

13.5.1 General

- Take a thorough history and examine the patient.
- Rapid treatment is essential, and should not be delayed.
- Search for and treat precipitating factors, e.g. exclude acute myocardial ischaemia.
- Prophylactic heparin is essential.
- Insert a nasogastric tube if the patient is comatose or has gastric dilatation, to prevent aspiration.
- 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.

13.5.2 Investigations

The following special investigations should be performed:

- Blood tests:
  - Glucose, urea and electrolytes, full blood count and differential, and glycated haemoglobin (HbA_{1c})
  - Venous blood gas
  - Plasma ketones.
- Urine tests:
  - Dipstick test for nitrites, blood, protein, and ketones
  - 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,[1] and thereafter 250-500 ml per hour. The aim is to replace 50% of the fluid

Table II. Laboratory findings in hyperglycaemic emergencies

	Diabetic ketoacidosis			Hyperglycaemic hyperosmolar state
	Mild	Moderate	Severe	
Plasma glucose (mmol/l)	> 13.9	> 13.9	> 13.9	> 33.3
Serum HCO_3 (mmol/l)	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 = $Na^+ - (Cl^- + HCO_3^-)$
Osmolality = $2(Na^+ + K^+)$ + urea + glucose

deficit during the first 12 hours after presentation, and the remainder within the next 12-16 hours.[2] Normal saline or Ringer's lactate are good choices for initial fluid resuscitation. Hyperglycaemia is corrected faster than ketoacidosis,[1] and 5% dextrose solution should be used once the glucose falls to < 14 mmol/l to prevent hypoglycaemia. If hyperchloraemic 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

Regular soluble insulin used intravenously is preferred for the treatment of hyperglycaemic emergencies. Serum potassium should always be checked before insulin infusion.

The most commonly used regimen for a patient admitted to a general ward is a loading bolus of 10 units IV, followed by hourly boluses of 10 units IV. This is based on a dose of 0.14 units/kg/hour in a 70 kg patient.[3] For patients admitted to an intensive care unit, a continuous insulin infusion at a rate of 0.14 units/kg/hour may be used.[1] In both cases, capillary glucose should be measured hourly to detect and prevent hypoglycaemia.

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

- Blood glucose < 15 mmol/l
- pH > 7.3
- Bicarbonate > 15 mmol/l
- The patient is fully conscious.

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.[1]

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

Important: Do not administer > 20 mmol KCl per hour

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 hypoglycemia, or rate of recovery from ketoacidosis.[4,5,6] There are no prospective randomised studies that have used bicarbonate in patients with a pH < 6.9. To date, the evidence does not justify the use of bicarbonate in the treatment of DKA.[7]

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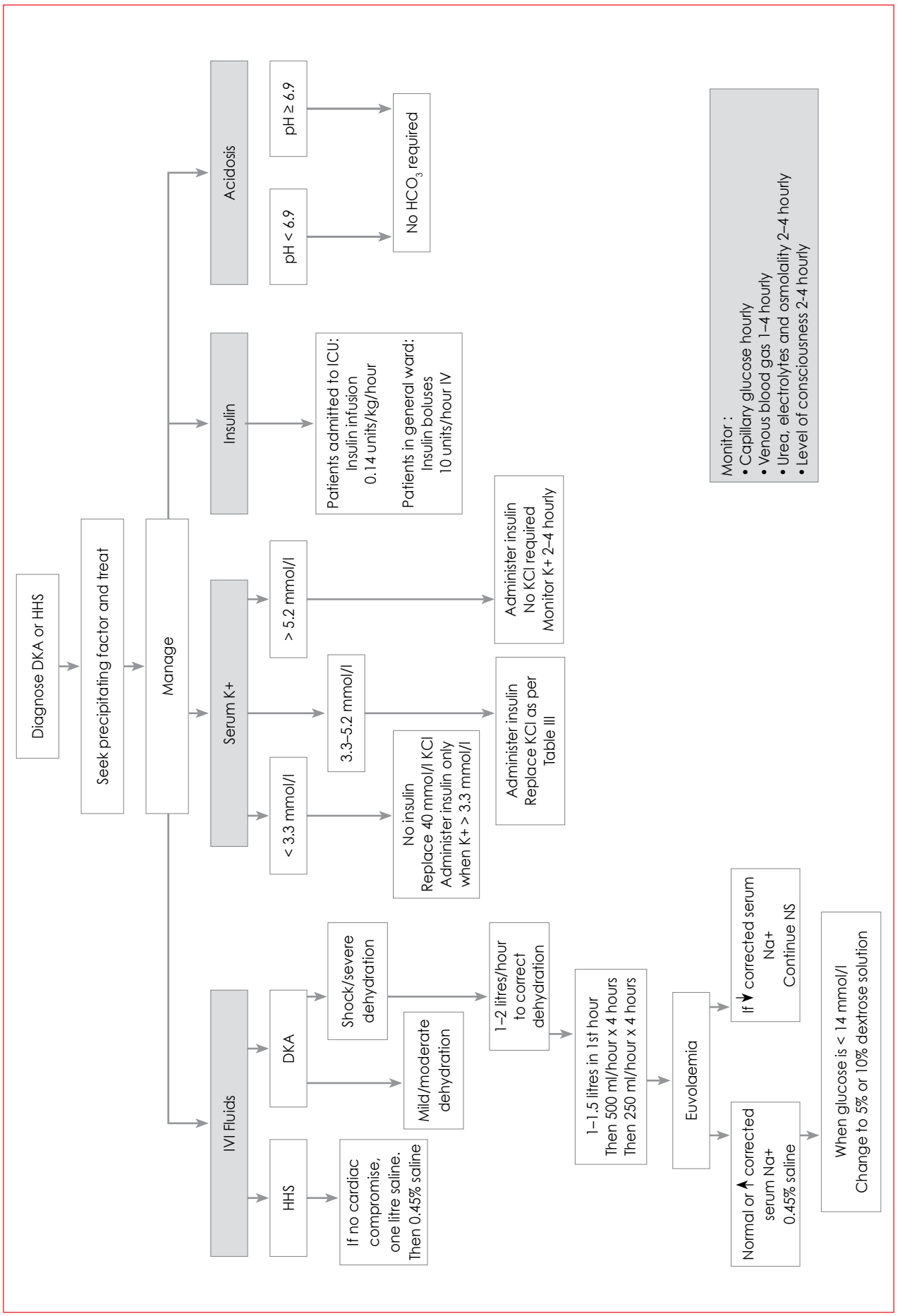
Diagnose DKA or HHS
Seek precipitating factor and treat
Manage
IVI Fluids
DKA
Shock/severe dehydration
Mild/moderate dehydration
HHS
If no cardiac compromise, one litre saline. Then 0.45% saline
1–2 litres/hour to correct dehydration
1–1.5 litres in 1st hour
Then 500 ml/hour x 4 hours
Then 250 ml/hour x 4 hours
Euvolaemia
If ↓ corrected serum Na+ Continue NS
Normal or ↑ corrected serum Na+ 0.45% saline
When glucose is < 14 mmol/l
Change to 5% or 10% dextrose solution
Serum K+
< 3.3 mmol/l
No insulin
Replace 40 mmol/l KCl
Administer insulin only when K+ > 3.3 mmol/l
3.3–5.2 mmol/l
Administer insulin
Replace KCl as per Table III
> 5.2 mmol/l
Administer insulin
No KCl required
Monitor K+ 2–4 hourly
Insulin
Patients admitted to ICU:
Insulin infusion
0.14 units/kg/hour
Patients in general ward:
Insulin boluses
10 units/hour IV
Acidosis
pH < 6.9
pH ≥ 6.9
No HCO_3 required
Monitor :
• Capillary glucose hourly
• Venous blood gas 1–4 hourly
• Urea, electrolytes and osmolality 2–4 hourly
• Level of consciousness 2-4 hourly

14. In-hospital management of diabetes

The management of hyperglycaemia in hospitalised patients differs from general outpatient management principles. Furthermore, hospitalised patients represent a heterogenous group, including medical and surgical patients who may or may not be critically ill. The focus is on the definition of hyperglycaemia, targets for control in the different groups of hospitalised patients, and the use of insulin therapy. The purpose of this section is to provide a guide to the selection and implementation of antihyperglycaemic therapy in hospitalised patients.

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14.1. In-hospital hyperglycaemia

Hyperglycaemia is a frequent occurrence in hospitalised patients, and has been reported to be the fourth most common condition listed on all hospital discharge forms.[1] It can occur in patients with or without diabetes mellitus (diabetes).[2,3] but many patients with in-hospital hyperglycaemia (IHH) often remain undiagnosed. However, even when patients are assessed for hyperglycaemia, they may not be treated optimally.[4]

IHH in the absence of diabetes has been labelled "stress hyperglycaemia" and is often overlooked by many clinicians as a condition that requires medical management. Stress hyperglycaemia has traditionally been thought to be a physiological process, and perhaps even be beneficial. However, this myth has been dispelled by overwhelming evidence indicating that IHH is associated with adverse clinical outcomes and increased mortality.[2,5,6]

Hospital hyperglycemia has been shown to be correlated with the length of hospitalisation, number of rehospitalisations and 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, and the conditions has also been demonstrated to potentiate coagulation and increase the risk of thrombosis, with exacerbation of these effects in the presence of systemic inflammation.[7-9]

The management of hyperglycaemia in the hospital can be challenging, as many factors can impact on the safety profiles of antihyperglycaemic drugs or exacerbate hyperglycaemia in patients known to have diabetes. The hospital environment is associated with variations in nutritional intake, changes in consciousness related to illness or anaesthesia, and the development of renal dysfunction. Therefore, institution or adjustment of therapy is crucial in all patients with IHH, even among those known to be previously well controlled on antihyperglycaemic therapy.

14.2 Definition and aetiology of hyperglycaemia in hospital

A consensus statement on in-patient glycaemic control by the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) defines hyperglycaemia as blood glucose level > 7.8 mmol/l. In patients without a previous diagnosis of diabetes, elevated blood glucose may be due to stress hyperglycemia, a condition that can be established by a review of prior medical records or measurement of glycated haemoglobin A_{1c} (HbA_{1c}).[2]

The literature on hospitalised patients with hyperglycemia typically describes three categories:

1. Medical history of diabetes: Diabetes has been previously diagnosed and acknowledged by the patient's treating physician.
2. Unrecognised diabetes: Hyperglycemia (fasting blood glucose ≥ 7 mmol/l, or random blood glucose ≥ 11.1 mmol/l) occurring during hospitalisation, and confirmed as diabetes after hospitalisation by standard diagnostic criteria, but not recognised as diabetes by the treating physician during hospitalisation.
3. Hospital-related hyperglycemia: Hyperglycemia (fasting blood glucose ≥ 7 mmol/l, or random blood glucose ≥ 11.1 mmol/l) occurring during hospitalisation, but that reverts to normal after hospital discharge.[10]

14.2.1 Role of HbA_{1c} testing

It may not be possible to differentiate between unrecognised diabetes and hospital-related hyper-

glycaemia (stress hyperglycaemia) at the bedside. However, HbA_{1c} measurement provides a useful indicator of exposure to hyperglycaemia over the previous three months. Therefore, normal HbA_{1c} in this setting would argue against unrecognised diabetes, and would favour instead a diagnosis of stress hyperglycaemia. Elevated HbA_{1c}, however, would suggest unrecognised diabetes. Although distinguishing between the different types of IHH would not largely affect management principles in the acute setting, the major implication of elevated HbA_{1c} is that patients would likely require ongoing antihyperglycaemic therapy upon discharge from hospital, either oral therapy or injected insulin. In contrast, normal HbA_{1c} levels would suggest that the hyperglycaemia may likely resolve following the acute illness or upon discharge from hospital. Therefore, it is recommended that HbA_{1c} testing be performed in all patients with IHH at the time of first detection.

14.3 In-hospital use of oral agents

In general, oral agents are considered unsuitable for in-hospital management of hyperglycaemia, whilst insulin is the favoured choice for treatment. Nevertheless, there are situations in which oral agents would be acceptable. This would include 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] However, despite the continued practice of administering oral agents in specific in-hospital instances, there are no published data on efficacy, neither are there any data on the safety of oral agents and injectable non-insulin therapies such as glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Sulphonylureas are insulin secretogogues that have been associated with severe and prolonged hypoglycaemia in patients with reduced or limited oral intake.[11] Thiazolidinediones are 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 antihyperglycaemic therapy in such instances. Metformin is also contraindicated in patients scheduled to undergo imaging studies requiring radio-contrast.

Oral agents can also not 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 patients with mild hyperglycaemia, or those who used these agents as outpatients.[5,10]

14.4 In-hospital use of insulin

In the hospital setting, insulin therapy is the preferred method of glycaemic control in the majority of clinical situations.[2] Insulin therapy forms the basis of treatment of IHH, because 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 regular 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-blous therapy for glycaemic control, but lack the flexibility of basal-bolus therapy, requiring strict adherence to scheduled meals. IV insulin therapy can also be used in specific circumstances, and 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 actions as ultra-short acting insulin analogues. The more rapid-acting insulin analogues, such as insulin aspart, lispro and glulisine, which can be injected just a few minutes before the meal, would be an advantage in the hospital setting where the timing of meals cannot be controlled by the patient and may differ from day to day.

14.5 Glucose monitoring

There are no data to support specific recommendations regarding glucose monitoring. Bedside blood-glucose monitoring is a useful tool to monitor response to therapy and helps to guide titration of antihyperglycaemic therapy, especially insulin dosing. In addition, glucose monitoring is vital in detecting hypoglycaemia, which is

an obstruction to the achievement of good glycaemic control and an important cause of morbidity. The frequency and timing of bedside blood-glucose monitoring must be individualised. Healthcare institutions should have standardised treatment protocols that address mild, moderate and severe hypoglycaemia. Healthcare workers should be educated about factors that increase the risk of hypoglycaemia, such as a sudden reduction in oral intake or discontinuation of enteral or parenteral nutrition.

14.6 Targets for glucose control

The 2009 AACE and ADA consensus statement on in-patient glycaemic control provides guidelines regarding targets for control among in-patients with hyperglycaemia. It is acknowledged that the targets recommended for critically ill patients are derived from the available evidence. However, with respect to non-critically ill patients, there are no prospective, randomised, controlled trial data available and recommendations are based on clinical experience and judgement.[2]

14.6.1 Glycaemic targets in critically ill patients

Insulin therapy should be initiated for treatment of 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. Frequent glycaemic monitoring guides glycaemic management and minimises the risk of hypoglycaemia. Targets < 6.1 mmol/, however, are not recommended. Ideally, IHH management in the intensive care unit (ICU) or high care should be attained with an insulin infusion protocol that demonstrates safety and efficacy.

14.6.2 Glycaemic targets in non-critically ill patients

There is no clear evidence for specific blood glucose goals. Fasting and preprandial blood glucose targets generally should be < 7.8 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.

14.7 IHH in non-critically ill patients

As has been mentioned before, insulin is the preferred antihyperglycaemic therapy for in-hospital use. Oral agents are generally considered unsuitable for a number of reasons, including greater risk of side-effects such as hypoglycaemia (sulphonylureas), delayed onset of action and inability to titrate the oral agent to target. Nevertheless, there are situations in which oral agents would be acceptable. This would include 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]

Stable patients with type 2 diabetes who use insulin at home should continue their pre-admission insulin regimen, with adjustment as needed. Non-critically ill patients on oral agents alone can safely be switched to insulin once admitted to hospital. Patients being switched from oral to insulin in hospital and who are eating regular meals are best treated by commencing scheduled basal and prandial insulin as separate components. Sliding-scale insulin therapy, though widely utilised, is not ideal and has been shown to be inferior to basal-bolus insulin therapyfor glucose control in non-critically ill patients with type 2 diabetes.[14]

Sliding-scale insulin therapy entails the injection of short- or rapid-acting insulin at predetermined intervals to manage hyperglycaemia, but is reactive in its approach to dealing with IHH, because hyperglycemia is only treated after it has occurred. This type of reactive approach to treatment is associated with higher rates of hyper- and hypoglycemia.[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 as well as more effective than sliding-scale insulin therapy with respect to glucose control in non-critically ill patients with type 2 diabetes.[14]

Scheduled SC insulin consisting of three separate components, basal, nutritional, and correctional (supplemental) doses, is the preferred method for achieving and maintaining glucose control in noncritically ill patients.[10] Prandial (nutritional) insulin provides enough insulin to cover the caloric intake at mealtimes and maintain euglycaemia, but does not cater for pre-meal hyperglycaemia. Therefore, using correction dose or "supplemental" insulin to correct pre-meal hyperglycaemia, in addition to scheduled prandial and basal insulin, is recommended.[10]

When deciding to initiate or continue insulin therapy, particular attention should be paid to basal requirements to ensure that fasting glucose is adequately addressed. Thereafter, nutritional factors should be taken into consideration, to decide on the dosing of short- or rapid-acting insulin to address the effects of a caloric load on glycaemia. Short- or rapid-acting insulin may be scheduled at mealtimes (prandial insulin) or when caloric exposure is anticipated, such as from IV fluids, total parenteral nutrition and enteral tube feeding.

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 of insulin as 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 total daily insulin 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 must be remembered that this initial dose of insulin, based on an estimate, does not usually provide ideal control, and that the response to insulin must be assessed quickly and on an ongoing basis, with appropriate titration of the insulin dose to achieve control. Depending on the glycaemic target selected, the insulin dose is then adjusted according to the results of bedside glucose monitoring, whilst also ensuring that the risk of hypoglycaemia is minimised.

In response to hyperglycaemia, small supplementary doses of regular insulin or a rapid-acting analogue can also be prescribed.[16] This insulin should be proportionate to the daily requirement and offered as a supplement to, not a replacement for, scheduled therapy.[17] For acutely ill patients, correction doses of regular insulin or a rapid-acting analogue may be given every four or two hours, respectively. The amount used as correction dose therapy may be used to guide required changes in scheduled insulin. 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 basal insulin, and the remaining amount divided among the meals and added to the prandial (nutritional) doses.

Prior to discharge, patients that were switched from oral therapy to insulin in hospital may be recommenced on their oral agents, provided they are clinically stable, do not have contraindications to the oral agents, and their eating patterns are regular.

14.7.1 Correction dose calculation

A correction dose is given in addition to any scheduled insulin doses, and is not intended to replace scheduled insulin, but rather augment it. In general, one unit of insulin lowers the blood glucose by about 2.8 mmol/l. However, responses to insulin may vary according to the level of insulin sensitivity. Determining the ideal correction dose requires calculation of the correction factor (CF) (also known as the insulin sensitivity factor), which takes into consideration the total daily insulin dose and type of insulin being utilised. It 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" (Table I). This is done by dividing either 100 (for rapid-acting insulin) or 85 (for short-acting insulin) by the patient's total daily insulin dose (TDD). The CF represents the expected fall in blood glucose for each unit of insulin administered.

For rapid-acting insulin analogues: CF = 100 ÷ TDD
For short-acting regular insulin: CF = 85 ÷ TDD

Table I: Calculation of the CF according to the "rule of 100" (rapid-acting insulin analogues) and "rule of 85" (short-acting insulin)

Total daily insulin dose	Correction factor (100 rule)	Correction factor (85 rule)
20 units	5.0	4.2
25 units	4.0	3.4
30 units	3.3	2.8
35 units	2.9	2.4
40 units	2.5	2.1
45 units	2.2	1.9
50 units	2.0	1.7
60 units	1.7	1.4
80 units	1.3	1.0
100 units	1.0	0.8

$$\text{Correction dose} = \frac{\text{(Actual blood glucose - target blood glucose)}}{\text{Correction factor}}$$

Correction doses should not usually be given within four hours of each other, and should be avoided if frequent or severe episodes of hypoglycaemia have occurred recently. Exercise may lower blood glucose, and this should also be considered before implementing a correction dose.

14.7.2 Patient receiving enteral feeds

Enteral feeding may cause or exacerbate IHH, with adverse outcomes. A systematic review and meta-analysis of studies of enteral nutritional support intervention in patients with diabetes showed that short- and long-term use of diabetes-specific formulas as tube feeds is associated with improved glycaemic control when compared to standard formulas.[18] Enteral feeds, often delivered via the nasogastric tube, may be administered on a continuous basis, as boluses or only nocturnally, in some instances. Glycaemic control in such patients may require different strategies, including the daily administration of long acting insulin analogues, eight-hourly administration of pre-mixed insulins, or 12-hourly administration of NPH insulin together with scheduled regular insulin administered six 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 for any reason. Therefore, protocols need to be in place that will enable staff to react to such occurrences promptly. If enteral feeding is stopped for whatever reason, insulin should also be immediately withheld and a 10% dextrose-containing infusion should be commenced to prevent hypoglycaemia until the effects of the insulin have worn off.

14.7.3 Patients receiving total parenteral nutrition

Total parenteral nutrition- (TPN) associated hyperglycaemia has also been linked with adverse clinical outcomes.[19] 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 glycaemic control has stabilised, IV insulin therapy can be stopped in favour of adding 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 total daily dose as basal insulin, and the remaining dose injected 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.

14.7.4 Patients being maintained nil per os

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. In addition, corrective doses of regular insulin can be given six hourly to maintain glycaemic targets (see the correction dose calculation). Patients being kept nil per os for prolonged periods should be maintained on a dextrose infusion to prevent hypoglycaemia.

14.7.5 Perioperative glycaemic management

Hyperglycaemia has been shown to affect immune function and may increase the risk for infection.[7-9] In patients undergoing surgical procedures, hyperglycaemia per se may adversely affect outcomes by increasing the risk of wound infection. Indeed, studies have shown that hyperglycaemia increases the risk of postoperative infections.[20] In surgical wards, postoperative wound infections have been shown to be the most common nosocomial infection, and an important contributor to morbidity and mortality. Furthermore, wound healing has also been shown to be adversely affected in animal models.

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

14.8 Critically ill patients

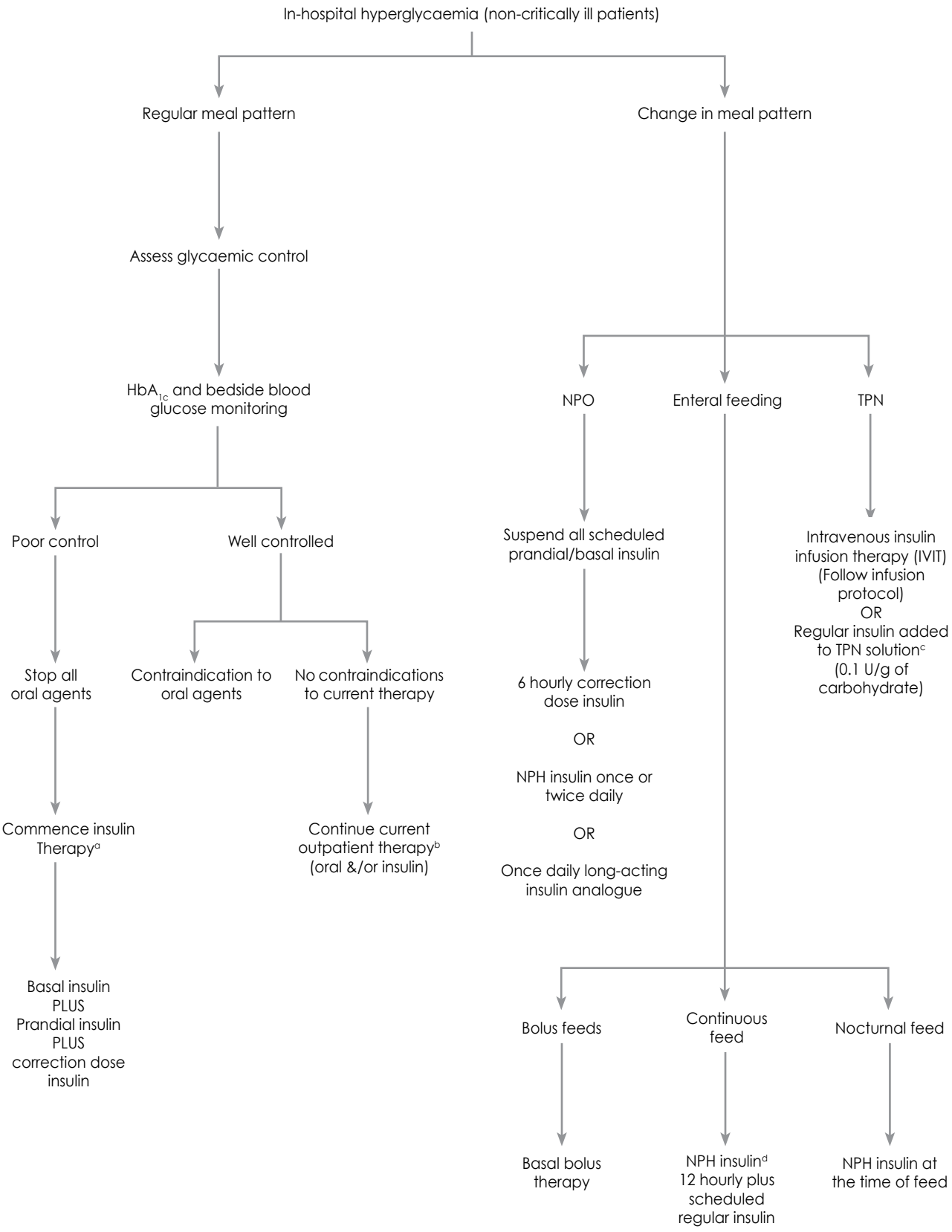
Acute hyperglycemia in the intensive care setting is not unusual and results from a number of factors, including stress-induced counter-regulatory hormone secretion, and is also possibly an effect of medications administered in the ICU.[21] Hyperglycemia in this setting has effects on multiple systems, including the cardiovascular, neurological and immune systems.[21] The results of early studies investigating the advantages of intensive insulin therapy in critical care patients were positive. Van den Berghe et al[22] demonstrated impressive benefits of intensive glycaemic control with IV insulin infusion, among predominantly surgical patients admitted to the ICU who required mechanical ventilation. A subsequent analysis of a heterogeneous ICU population with predominantly medical patients and utilising historical controls 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.[22]

However, more recent randomised, controlled studies in critically ill patients have not shown the substantial mortality benefits that were previously described with intensive glycaemic control. The largest randomised, controlled study undertaken to evaluate the benefits of intensive glycaemic control was the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, which included 6 104 critically ill patients. Patients were divided into 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, and 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 the median number of days spent in the ICU or the hospital and days on mechanical ventilation or renal replacement therapy. 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, such as length of

Table II: Insulin infusion protocol in the ICU

Treatment threshold	Blood glucose ≥ 10.0 mmol/l			
Treatment goal	Blood glucose 7.8-10.0 mmol/l			
Discontinue all other insulin orders				
Initiating the infusion	Set up an IV system by mixing 50 units of insulin in 100 ml of 5% dextrose water (0.5 units/ml). The system must be an infusion pump capable of infusing at rate changes of 0.5 ml/hour.			
Prime the system	Flush 50 ml of the solution through the tubing, to ensure saturation of all insulin-binding sites in the tubing			
Initial bolus and infusion rate:[24]				
Blood glucose	10.0-14.9 mmol/l	14.0-16.6 mmol/l	16.7-20.0 mmol/l	> 20.0 mmol/l
Bolus injection	4 units	6 units	8 units	10 units
Infusion rate	2 units/hour	3 units/hour	4 units/hour	5 units/hour
Infusion titration				
Blood glucose	*Current insulin infusion rate: 0-10 units/hour*		*Current insulin infusion rate: > 10 units/hour*[a]	
< 2.8 mmol/l	Stop the infusion Give 25 ml of 50% dextrose IV Check glucose in 15 minutes: - If glucose < 2.8 mmol/l, repeat 25 ml 50% dextrose IV, until glucose > 4.4 mmol/l - If glucose > 7.8 mmol/l, resume infusion at 50% of previous rate.			
2.8-4.4 mmol/l	Stop the infusion Give 10 ml of 50% dextrose IV Check glucose in 15 minutes: - If glucose < 4.4 mmol/l, repeat 10 ml 50% dextrose IV, until glucose > 4.4 mmol/l - If glucose > 7.8 mmol/l, resume infusion at 50% of previous rate.			
4.5-7.7 mmol/l	Stop the infusion Check glucose hourly until ≥ 7.8 mmol/l If glucose > 7.7 mmol/l, resume infusion, but reduce the previous infusion rate by 0.5 units/hour		Stop the infusion Check glucose hourly until ≥ 7.8 mmol/l If glucose > 7.7 mmol/l, resume infusion, but reduce the previous infusion rate by 1.0 units/hour	
7.8-8.9 mmol/l	Continue at the same rate - If glucose declines over three consecutive hours, reduce the infusion rate by 1.0 unit/hour[b] - If glucose increases over three consecutive hours, increase the rate by 1.0 unit/hour[c]		Continue at the same rate - If glucose declines over three consecutive hours, reduce the infusion rate by 1.5 unit/hour[b] - If glucose increases over three consecutive hours, increase the rate by 1.5 unit/hour[c]	
9.0-10.0 mmol/l	Continue at the same rate - If glucose declines over three consecutive hours, reduce the infusion rate by 1.0 unit/hour[b] - If glucose increases over three consecutive hours, increase the rate by 1.0 unit/hour[c]		Continue at the same rate - If glucose declines over three consecutive hours, reduce the infusion rate by 1.5 unit/hour[b] - If glucose increases over three consecutive hours, increase the rate by 1.5 unit/hour[c]	
> 11.1 mmol/l	Increase the insulin infusion rate by 4.0 units per hour.[c] If the infusion rate is at the maximal 24 units/hour, give an additional IV insulin bolus according to the initial insulin bolus injection scale (see above), but do not increase the infusion rate. If the glucose remains > 11.1 mmol/l despite insulin infusion at 24 units/hour plus an additional IV bolus, reconstitute the insulin in 0.9% saline.			
Glucose monitoring	Initially, monitor blood glucose hourly. (Finger prick or arterial samples, but do not rely on finger prick samples in hypotensive patients)			
	Once three consecutive blood glucose values are on target: monitor two hourly			
	Resume hourly glucose monitoring if: - Any change in the insulin infusion rate - Any change in the patient's clinical condition - Commencement or cessation of inotropic or steroid therapy - Commencement or cessation of renal replacement therapy - Commencement, change or cessation of nutritional support (i.e. TPN, enteral feeding)			
Discontinue the protocol when the patient has been placed on a regular diet or moved out of ICU or high care. In this case, obtain new orders for insulin administration, preferably using the basal-bolus regimen, from a member of the diabetes and endocrine unit.				

[a] Maximum infusion rate = 24 units/hour
[b] If there is > 50% decrease in glucose from the previous value, decrease the infusion rate by 50% and check the glucose in one hour
[c] If there is ≥ 1.7 mmol/l decrease from the previous value, do not increase the infusion rate



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: Alternative : Add 50% of total dose as regular insulin to TPN AND 50% given as Basal insulin subcutaneously
d: Alternative : Premixed insulin 8 hourly or Long Acting Insulin Analogue given daily

Figure 1: Algorithm for the management of in-hospital hyperglycaemia (IHH) in non-critically ill patients

stay in the ICU, total duration of hospitalisation, number of days of mechanical ventilation, and rates of positive blood cultures or red blood cell transfusion.

Although unexpected, 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, including the NICE-SUGAR study, showed a mortality benefit for intensive glycaemic control among surgical ICU patients only.[23] However, the meta-analysis also showed that intensive therapy was associated with a significantly higher risk of hypoglycaemia.

Critically ill patients in ICU and high-care settings are best managed with IV insulin therapy. However, IV insulin therapy requires more frequent blood glucose monitoring and titration of the insulin dose, depending on the insulin infusion protocol implemented. Before commencement of IV insulin therapy, clinicians should ensure that a well-validated insulin infusion protocol is selected and that regular blood-glucose monitoring is facilitated. Adequate numbers of trained nursing staff are needed to ensure successful implementation. Furthermore, nursing staff in the critical-care setting need to be well educated on specific protocols such as insulin titration and, most importantly, the management of hypoglycaemia. Table II is an example of an IV insulin therapy protocol.

Note:

- Maintain basal fluids at 83 ml/hour (1 992 ml/24 hours) in total, using 5% dextrose in water, saline or lactated Ringers solution
- A new insulin solution must be mixed every 24 hours.

Currently, the ideal target for blood glucose in perioperative patients with hyperglycaemia is unclear. There are no specific recommendations in surgical patients, and targets for control are the same as in non-surgical patients. In critically ill patients, it is recommended that glucose values be maintained between 7.8-10 mmol/l.[2] Although there is little evidence to support this, 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 hypoglyceamia. Targets < 6.1 mmol/l, however, are not recommended. In non-critically ill patients, fasting and preprandial blood glucose targets generally should be < 7.8 mmol/l, and random blood glucose values < 10 mmol/l. The main concern regarding perioperative glycaemic control is the occurrence of hypoglycaemia. Any treatment strategy should take into consideration the risks of hypoglycaemia, and the necessary staff and protocols should be in place to deal with hypoglycaemia.

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15. Obesity in type 2 diabetes

The aim of this section is to provide up-to-date guidelines on the management of obesity in patients with type 2 diabetes mellitus. Weight loss goals and current treatment options are covered, and there is specific emphasis on diet and exercise, behavioural therapy, pharmacotherapy and bariatric surgery.

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15.1 Weight-loss goals

The aim in patients with diabetes mellitus (diabetes) is to lose 5-10% of body weight, maintain weight loss and prevent weight regain. More weight loss, to the normal body mass index (BMI) is ideal, but not easily achievable.

The optimal rate of weight loss is 1-2 kg per month.

15.2 Diet and exercise

Quantity adjustments of the diet in terms of caloric restriction is most important for weight loss, more so than quality adjustments. However, quality is important for cardiovascular disease reduction. Optional diets include the low-fat, low-carbohydrate (may need to adjust hypoglycaemic therapy), and Mediterranean diets.

Very low-calorie diets (< 800 calories per day) should only be prescribed in very carefully selected patients, and then only at centres with experience, preferably as a part of bariatric surgery work-up.

Physical activity of moderate intensity for longer 225–420 minutes per week will result in 5-7.5 kg weight loss. A dose-response relationship exists. To prevent weight gain of > 3% in adults, moderate exercise for 150-250 minutes per week is required. For weight maintenance after weight loss, 200-300 minutes of exercise per week is required.

Resistance training has not been shown to be effective for weight loss in studies, 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 improves chronic disease risk factors.

15.3 Behavioural therapy

Behavioural therapy is important for supporting weight loss, and should involve:

- Developing specific and realistic goals that can easily be measured.
- Developing a reasonable plan for reaching those goals and preventing relapse.
- Making incremental changes, rather than radical changes.

15.4 Pharmacotherapy

Currently, only orlistat is approved as pharmacotherapy for weight loss. It can be prescribed for patients with diabetes with BMI ≥ 27 kg/m^2, and in those with pre-diabetes with BMI ≥ 30 kg/m^2.

15.5 Bariatric surgery

Bariatric surgery should be considered for patients 18 years and older with BMI ≥ 35 kg/m^2, and who have been diagnosed with diabetes. The surgery must be performed in an experienced multidisciplinary unit, and the team should consist of an endocrinologist, diabetes specialist, psychiatrist, dietitian, biokineticist and surgeon. Regular, structured follow-up is essential.

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

It is important to recognise that type 2 diabetes mellitus is in essence a vasculopathic disorder that affects 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 should, therefore, be considered a coronary artery disease risk equivalent and dyslipidaemia and other cardiovascular risk factors should be looked for and aggressively treated in every patient with diabetes

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16.1 Macrovascular disease

The risk of CVD for people with type 2 diabetes is increased by two to three times for men and three to five times for women compared with people without diabetes. Outcomes following myocardial infarction, stroke or revascularization are also worse in diabetics compared to normoglycaemic 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. Table 1 summarises the traditional modifiable risk factors for CVD and the recommended target values in diabetes.

16.1.1 Estimating CVD risk in type 2 diabetes

Estimating future CVD risk can be a useful adjunctive tool for planning comprehensive management and counseling patients. There are a variety of risk-scoring systems available for estimating an individual patient's future risk for coronary heart disease (CHD). The UKPDS Risk engine uses the traditional risk factors to estimate the 10 year risk of CHD specifically in patients with type 2 diabetes (available for download at http://www.dtu.ox.ac.uk/riskengine/download.php). 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.

16.2 The metabolic syndrome

The metabolic syndrome, or insulin resistance syndrome, has become one of the major public health challenges worldwide. 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.

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

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

[a] The LDL-cholesterol goal is < 2.5 mmol/l in patients with type 2 diabetes who meet all of the following criteria:
- No cardiovascular disease and no chronic kidney disease
- Less than 40 years old OR duration of diabetes less than 10 years
- No other cardiovascular risk factors

LDL = low density lipoprotein; HDL = high density lipoprotein

The metabolic syndrome increases the risk of developing diabetes approximately fivefold, and doubles the risk of atherosclerotic cardiovascular disease. Features characteristic of the syndrome include abdominal obesity, atherogenic dyslipidaemia (elevated serum triglyceride and lowered HDL cholesterol), hypertension and elevated fasting glucose. Other ancillary features 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 III. 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 IV.

Table III: Harmonised criteria for the clinical diagnosis of the metabolic syndrome

Measure	Categorical cut points
Elevated waist circumference	Population- and country-specific definitions (Table IV)
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

Table IV: Population- and country-specific definitions of elevated waist circumference

	Men	Women
USA	≥ 102 cm	≥ 88 cm
Europid[a]	≥ 94 cm	≥ 80 cm
Asian	≥ 90 cm	≥ 80 cm
Chinese	≥ 85 cm	≥ 80 cm
Japanese	≥ 85 cm	≥ 90 cm

[a] Used in sub-Saharan Africa

Insulin sensitisers, such as metformin, 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 the section on the prevention/delay of diabetes).

16.3 Diabetic dyslipidaemia

Atherosclerosis accounts for up to 70% of all diabetic mortality in white, coloured 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.

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. The most frequently encountered lipid disturbances in type 2 diabetes are increased serum triglycerides and decreased HDL cholesterol.

16.3.1 Goals of therapy

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

* The LDL-cholesterol goal is < 2.5 mmol/l in patients with type 2 diabetes who meet all of the following criteria:

a. No cardiovascular disease and no chronic kidney disease
b. Less than 40 years old OR duration of diabetes less than 10 years
c. No other cardiovascular risk factors

16.3.2 Monitoring serum lipids

A full fasting lipid profile (10 hour fast evaluating total cholesterol, triglycerides, HDL cholesterol and calculated LDL cholesterol) should be done when first evaluating the diabetic patient. Subsequent evaluation can be targeted at the identified abnormalities and the treatment target; e.g. in a patient without hypertriglyceridaemia and an adequate HDL cholesterol LDL cholesterol is the sole treatment target and follow-up evaluation with directly measured LDL cholesterol only (if available) may be adequate. Patients with more complex abnormalities will require more detailed follow-up evaluation (repeated fasting lipid profiles).

If the results of the fasting lipid profile 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. Three monthly follow-up measurements is required during the titration phase of lipid-lowering therapy.

16.3.3 Nonpharmacological therapy

Diet is the cornerstone of therapy. Hypertriglyceridaemia usually responds particularly well to dietary triglyceride restriction. All diabetic patients should receive standard advice on healthy eating habits and preferred food choices from a nutritionist/dietician, with particular emphasis on:

- 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: Fat intake should be limited to < 30% of daily energy content, and should be equally divided between saturated, polyunsaturated and monounsaturated fats. Saturated fat intake should be less than 7% of total caloric intake and trans fat consumption should be minimized. Cholesterol intake should be restricted to < 300 mg per day.
- Fibre: The fibre content of the diet should be increased aiming for an intake of around 14 g per 1000kcal 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.

Secondary causes of hyperlipidaemia (e.g. hypothyroidism, renal disease and alcohol abuse) must always be excluded.

16.3.4 Pharmacological therapy

16.3.4.1 General recommendations

- 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.
- 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, these patients should be referred for specialist assessment as there is currently considerable uncertainty regarding optimal lipid management in diabetes beyond LDL cholesterol lowering.
- 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/1.73 m^2).
  - Are 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 micro- or macroalbuminuria.
- 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.
- 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 > 2.5 mmol/l.
- Specialist referral should occur when triglyceride levels > 5 mmol/l in the controlled diabetic, or > 15 mmol/l before treatment.

16.3.4.2 HMG-CoA reductase inhibitors (atorvastatin, lovostatin, pravastatin, simvastatin, rosuvastatin)

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. Statins are safe in renal failure.

16.3.4.3 Fibric acid derivatives (bezafibrate, fenofibrate, gemfibrozil)

Fibrates are indicated when there is severe hypertriglyceridaemia (> 10-15 mmol/l) to reduce the risk of acute pancreatitis. The fibrates decrease LDL cholesterol by 10-15% and triglycerides by 30-50%, and increase HDL cholesterol by 10-15%. 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.

16.3.4.4 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.

16.3.4.5 Bile acid sequestrants (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.

16.3.4.6 Niacin

Niacin lowers triglycerides, lipoprotein(a), LDL cholesterol and increases HDL cholesterol. Its use is associated with flushing and it may impair glycaemic control at high doses. Niacin is a theoretically attractive agent for the management of diabetic dyslipidaemia and did reduce CVD outcomes as monotherapy in earlier studies of non-diabetic cohorts. However, a recent study of niacin in combination with a statin was stopped for futility. The results of a large outcome study are awaited to finally determine the role of niacin.

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17. Aspirin therapy in diabetes

Until recently, people with diabetes mellitus without cardiovascular disease were thought to have the same 10-year risk as people without diabetes who had had a cardiac event. This has now been shown not to apply to those at lowest risk. Which patients with diabetes will benefit from aspirin prophylaxis?

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The benefits of providing aspirin therapy for secondary prevention of cardiovascular disease are well established.

Aspirin is associated with a significant increase in gastrointestinal and, to a lesser extent, intracranial bleeds. For primary prevention, aspirin therapy is therefore not beneficial in all patients with diabetes mellitus (diabetes), for example, in younger patients without significant risk factors (i.e. < 5% risk of cardiovascular disease over next 10 years). Aspirin should be given to all patients with diabetes with a10-year risk of cardiovascular disease > 10%, unless there are serious contraindications to therapy. In those at intermediate risk (5-10%), aspirin use is decided on an individual basis. The best dose of aspirin has not been established (range 75 mg to 300 mg once daily).

Table I provides a simple plan for calculating risk of cardiovascular disease.

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Table I: Calculation of 10-year cardiovascular risk

	Low risk (< 5%)	High risk (> 10 %)
Age Female Male	 < 60 years < 50 years	 > 60 years > 50 years
Risk factors Family history Smoker Raised blood pressure Raised cholesterol Lowered glomerular filtration rate (60-90 ml/minute)	None	One or more

18. Management of hypertension in patients with type 2 diabetes mellitus

Patients with type 2 diabetes mellitus and concomitant hypertension have a high risk of developing macro- and microvascular complications. Treatment of hypertension in these patients is associated with a consistent reduction in macrovascular disease, and a variable reduction in microvascular disease. The targets for treatment and drugs of choice have been revised in accordance with recent published evidence.

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18.1 Diagnosis of hypertension

Systemic hypertension is common in type 2 diabetes mellitus (diabetes) and will affect the majority of patients at some point in the course of their disease. 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 > 140/80mmHg on two separate days. Ambulatory BP measurement (ABPM) should be utilised in selected cases when "white-coat hypertension" is suspected.

18.2 Target for treatment

The BP target in most patients with type 2 diabetes is ≤ 140/80 mmHg and ≥ 120/70 mmHg.

BP lowering in hypertensive patients is associated with benefits in cardiovascular morbidity and mortality. The previous conventional target BP for type 2 diabetes was ≤ 130/80mmHg. However, the systolic target of 130 mmHg has always been an extrapolated one with no direct evidence of benefit from randomised trials. A recent comprehensive review on the subject concluded that "…on the basis of available evidence from placebo-controlled trials, randomized trials, and achieved BP analyses, the target BP levels recommended in current guidelines are not supported for the prevention of macrovascular outcomes in patients with diabetes". A J-shaped relationship exists between BP and cardiovascular risk, which seems to be most profound in patients with cardiovascular disease. Therefore, the SEMDSA revised BP target in most patients with type 2 diabetes is ≤ 140/80 mmHg and ≥ 120/70 mmHg.

18.3 Treatment algorithm

Figure 1 provides an algorithm for the treatment of hypertension in patients with type 2 diabetes. Angiotensin receptor blockers (ARBs) must replace angiotensin converting enzyme inhibitors (ACEIs) if patients are intolerant to the latter. Normal values for urinary albumin: creatinine ratio (ACR) are discussed in the section on chronic kidney disease.

18.4 Additional treatment instructions for the healthcare provider

Renal function should be monitored. If the potassium level is elevated, or the creatinine level doubles, therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers should be stopped and the patient should be referred for specialist investigation and management.

Treatment should be adjusted at each visit at which the BP is not at target, i.e. ≤ 140/80 mmHg and ≥ 120/70 mmHg.

If the patient is planning pregnancy, therapy should be maintained with a dihydropyridine calcium-channel blocker, and not an ACE inhibitor, ARB or diuretic. Once pregnancy has been confirmed, therapy should be switched to methyldopa and the patient should be referred to an antenatal unit equipped to manage high-risk pregnancies.

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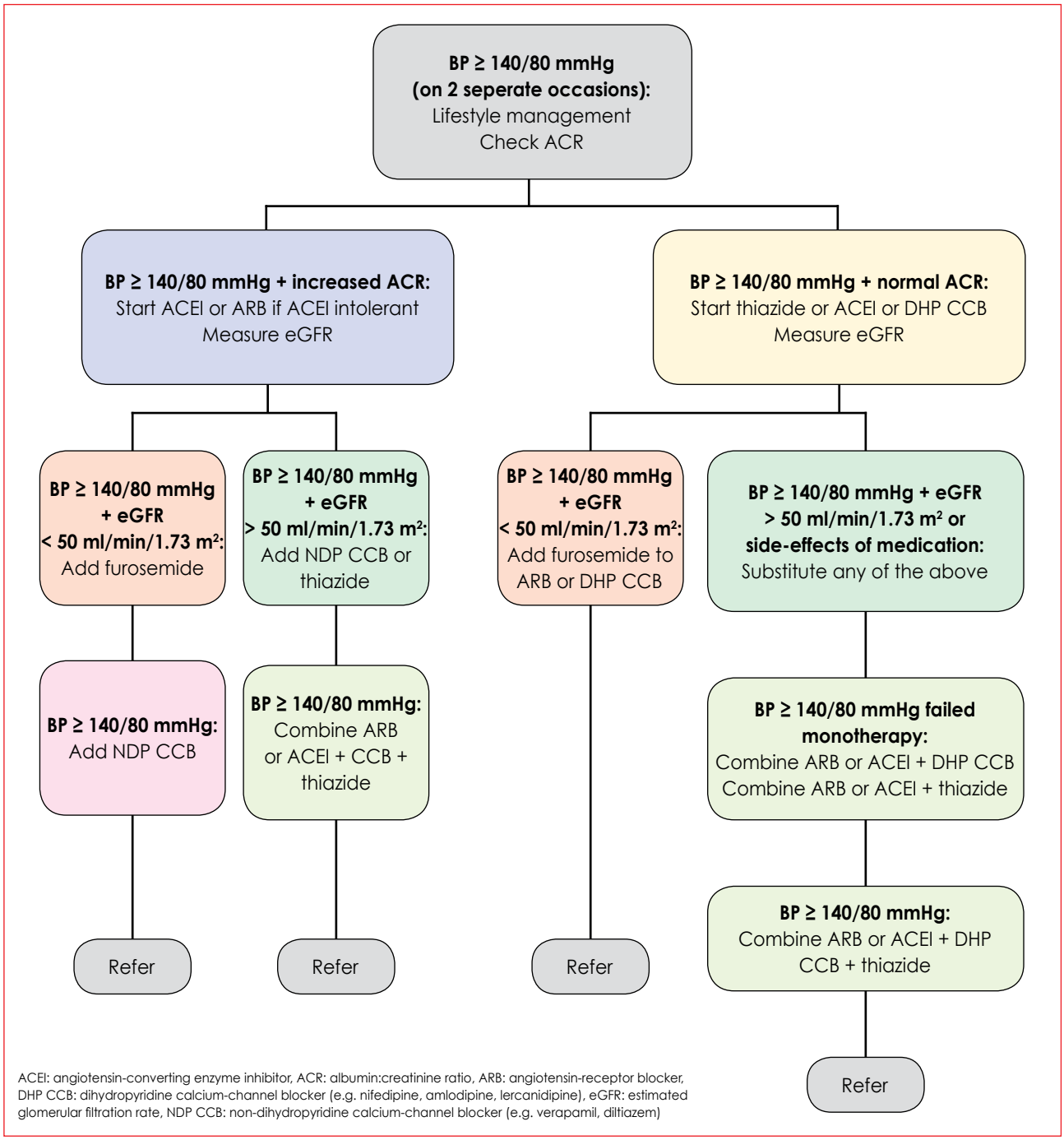

ACEI: angiotensin-converting enzyme inhibitor, ACR: albumin:creatinine ratio, ARB: angiotensin-receptor blocker, DHP CCB: dihydropyridine calcium-channel blocker (e.g. nifedipine, amlodipine, lercanidipine), eGFR: estimated glomerular filtration rate, NDP CCB: non-dihydropyridine calcium-channel blocker (e.g. verapamil, diltiazem)

Figure 1: Treatment algorithm for hypertension in patients with type 2 diabetes

outcomes in the diabetes cohort of the INternational VErapamil SR-Trandolapril study. Hypertension. 2004;44:637-642.

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19. Screening for and management of chronic kidney disease in adults with diabetes mellitus

Diabetic nephropathy is a frequent but potentially preventable long-term complication of diabetes mellitus which is responsible for significant morbidity and mortality, and is also a monetary burden on the healthcare system. Regular follow-up of all patients and adhering to a strict treatment protocol will go a long way towards preventing or retarding the progression of diabetic nephropathy.

JEMDSA 2012;17(2):S63-S66

19.1 Prevalence of chronic kidney disease in diabetes

Diabetes mellitus (diabetes) is the leading cause of end-stage renal disease in Europe and the USA.[1] Approximately 40% of patients with diabetes will develop chronic kidney disease (CKD).[1]

19.2 Progression of classic diabetic nephropathy

Classic diabetic nephropathy progresses from subclinical disease to the earliest clinically detectable stage, which is characterised by persistent proteinuria (Figure 1).[2]

19.3 Precautions before screening

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 estimated glomerular filtration rate (eGFR) (e.g. dehydration, hypovolaemia), and acute renal failure on clinical grounds before each screening and urine dipstick testing.[2]

19.4 Patients who must be screened

- Patients with type 1 diabetes of more than five years' duration[3]
- Patients with type 2 diabetes at diagnosis.[4]

19.5 Method of screening

Figure 2 illustrates how screening should be done.

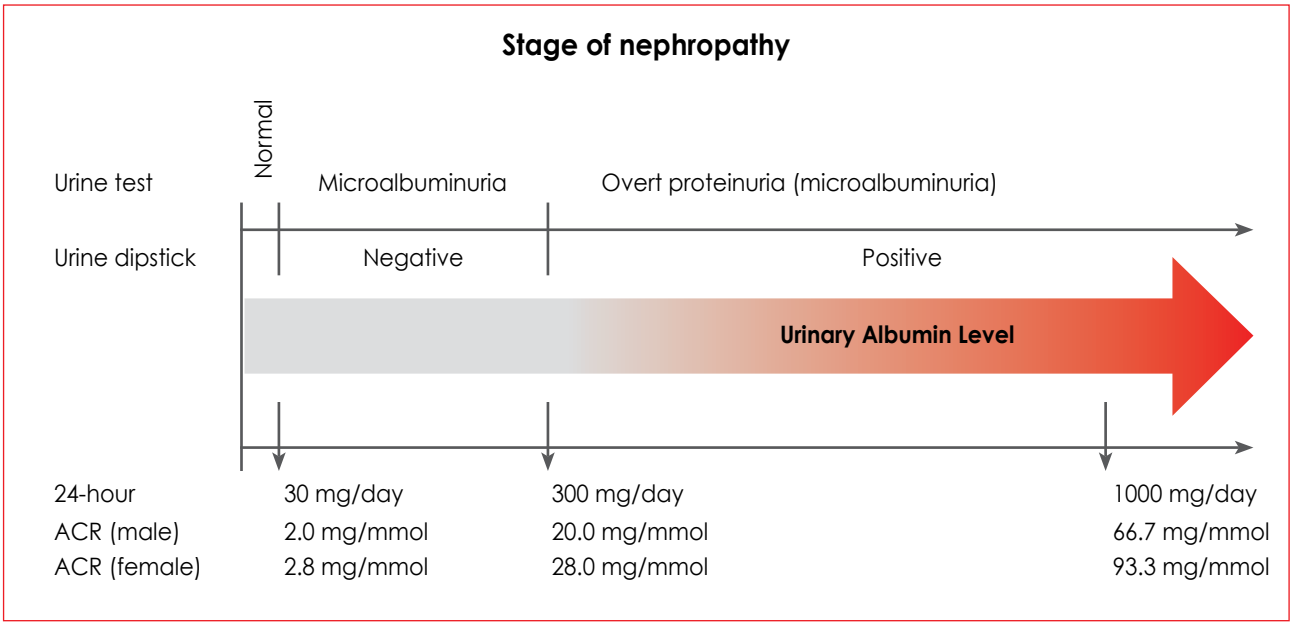

Figure 1: Progression of classic diabetic nephropathy[2], illustrating the levels of albuminuria and urinary albumin: creatinine ratio (ACR)

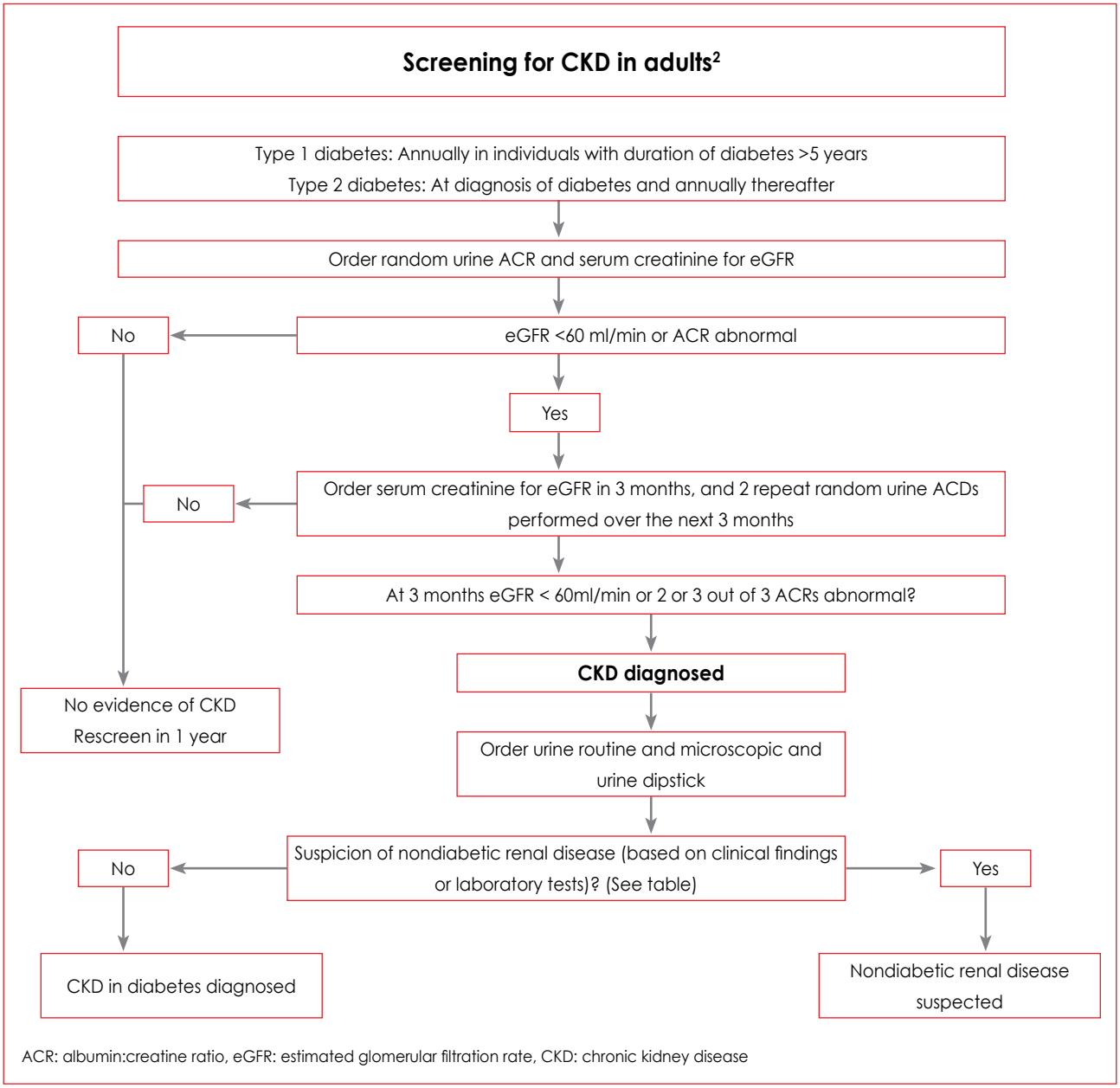

Figure 2: Screening for CKD in adults[2]

Screening for CKD in diabetes requires a minimum of two laboratory tests:[2]

- A random urine sample, for determination of the albumin-to-creatinine ratio (ACR)
- A serum creatinine concentration, for conversion into the eGFR.

Both tests are routinely performed by a laboratory such as the National Health Laboratory Service (NHLS). Approximately 20 ml of urine, collected at any time of the day, is required for the ACR, and a 10 ml non-fasting specimen of clotted blood is required for the serum creatinine measurement. To calculate the eGFR, the laboratory also needs the patient's age, sex and race.

19.6 Frequency of screening and testing

- If the ACR value lies within the normal range and the eGFR > 60 ml/minute: annually.[2]
- If the ACR is abnormal or the eGFR ≤ 60 ml/minute, the serum creatinine must be repeated once within the following three months and the ACR must be repeated twice within the same period. At three months:[2]
  - If the ACR value lies within the normal range and the eGFR > 60 ml/minute: repeat screening annually.
  - If the ACR is abnormal in two out of three tests or if the eGFR ≤ 60 ml/minute, the presence of CKD is confirmed. The patient must be referred

for further work-up to exclude nondiabetic renal disease or to confirm CKD in diabetes.

19.7 Management of CKD in diabetes

The best possible glycaemic control and, if necessary, intensive diabetes management should be instituted in people with type 1[5] or type 2[6] diabetes, for the prevention of the onset and delay in progression to CKD.

Blood pressure should be controlled and other cardiovascular risk factors (e.g. smoking, dyslipidaemia) should be aggressively managed.

A random urine ACR and serum creatinine converted into eGFR must be performed at least every six months in patients with diabetes and CKD, to monitor disease progression and response to treatment.[2]

Adults with diabetes and persistent albuminuria (ACR > 2.0 mg/mmol in men and > 2.8 mg/mmol in women) should be prescribed an angiotensin-converting enzyme (ACE) inhibitor to delay progression of CKD,[7] even in the absence of hypertension.[2] ACE inhibitors such as enalapril (10-20 mg daily), perindopril (2 mg daily), ramipril (2.5-10 mg daily) and lisinopril (5-20 mg daily) were used in clinical trials.[8] Note that microalbuminuria is also an important risk factor for cardiovascular disease.

Coughing, the most common side-effect associated with ACE inhibitors, may respond to a decreased dose or may spontaneously disappear after a few months. Angioneurotic oedema, a life-threatening adverse effect if the glottis or larynx is affected, occurs in a minority of patients, and more commonly in black patients.[9]

Angiotensin-receptor II antagonists (ARBs), such as losartan (50-100 mg daily)[10] or irbesartan (150-300 mg daily),[11] should be considered when ACE inhibitors cannot be tolerated.

Patients should be monitored with follow-up serum creatinine and potassium levels within one to two weeks of initiation of an ACE inhibitor or ARB or titration of dose, for significant worsening of renal function or for the development of hyperkalaemia.[2] Serum creatinine may increase by up to 30% above baseline after initiation of an ACE inhibitor or ARB.[12] In such an event, the ACE inhibitor or ARB should be discontinued. When renovascular hypertension is suspected, patients should be referred to a physician experienced in renal medicine.[2]A potassium-restricted diet should be considered in case of a mild to moderate increase in serum potassium concentration. Non-potassium sparing diuretics, such as hydrochlorothiazide or furosemide, may also be considered.[2]

ACE inhibitors should be initiated with great care if the eGFR is < 30 ml/minute, or referral to a physician experienced in renal medicine should be considered.[2]

ACE inhibitors and ARBs are contraindicated in pregnancy, because of potential teratogenicity.[13]

When hypovolaemia is present or suspected, ACE inhibitors, ARBs and diuretic therapy should be stopped to prevent acute renal failure.[2]

In patients with diabetes, hypertension and proteinuria, non-dihydropyridine (non-DHP) calcium-channel blockers, such as diltiazem and verapamil, could be considered when ACE inhibitors and ARBs are contraindicated.[14] Non-DHP calcium antagonists can be used alone or in combination with an ACE inhibitor or ARB.[15]

19.8 Referral for specialised renal care

Referral to a physician experienced in the management of renal disease should be considered when:[2]

- There is chronic, progressive loss of renal function, in spite of the suggested measures.
- The eGFR is < 30 ml/minute
- The ACR is persistently > 60 mg/ml.
- Blood pressure targets cannot be reached.
- Patients cannot tolerate ACE inhibitors or ARBs, as a result of hyperkalaemia or > 30% increase in serum creatinine within three months of initiating treatment with these agents.

19.9 Other causes of CKD in diabetes

More than 50% of people with diabetes and significant renal dysfunction, but with normal urinary albumin levels, have renal disease unrelated to classic diabetic nephropathy.[16] A cause other than classic diabetic nephropathy should be considered under the following circumstances:[2]

- Presence of extreme proteinuria (> 6 g/day)
- Persistent haematuria (micro- or macroscopic), or active urinary sediment
- Rapidly falling eGFR
- Low eGFR with little or no proteinuria
- Other complications of diabetes not present or not severe (e.g. diabetic retinopathy)
- Known duration of diabetes five years or less
- Family history of nondiabetic renal disease (e.g. polycystic kidney disease)
- Signs or symptoms of systemic disease.

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20. Screening for and management of retinopathy in adults with diabetes mellitus

Diabetic eye disease is a leading cause of visual impairment in the developing world, and is mainly comprised of diabetic retinopathy and cataract formation. Diabetic retinopathy is by and large preventable and/or treatable, while cataract surgery can now successfully be performed on a large scale. Stopping smoking and optimal glycaemic and blood pressure control will go a long way toward reducing the incidence of diabetic retinopathy. Regular and thorough eye examination through dilated pupils and testing of visual acuity should identify patients at risk of sight-threatening complications in time for appropriate referral to an ophthalmologist.

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20.1 Prevalence of diabetic retinopathy

Up to 40% of patients with diabetes mellitus (diabetes) have diabetic retinopathy, while 8% have sight-threatening retinopathy.[1]

20.2 Screening for diabetic retinopathy

The following patients should be screened:

- Patients 15 years and older with type 1 diabetes of five or more years' duration.[2]
- All patients with type 2 diabetes at diagnosis.[2]

20.3 Method of screening

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

- Indirect ophthalmoscopy (dilated slit-lamp ophthalmoscopy) by an ophthalmologist).[2]
- Direct ophthalmoscopy through dilated pupils by medical practitioners, optometrists and ophthalmologists.[2]
- Fundus photographic methods,[2] of which dilatation improves results.[3] This should be done on 35 mm film, digital images or Polaroid instant-film prints, with subsequent grading by trained individuals. The photograph should be evaluated by an ophthalmologist or medical doctor, nurse or optometrist properly certified by the Ophthalmological Society of South Africa (OSSA).[4]

Screening with a mobile fundus camera has improved the quality of care of diabetic patients and is feasible in the South African public sector, primary care setting.[5] Retinal photography has been found to be effective, acceptable and cost-effective.[6]

Since few primary healthcare nurses in South Africa are trained to screen for diabetic retinopathy, most patients at primary healthcare level will have to be referred to a skilled professional for evaluation.

The role of routine visual acuity testing as a screening tool for diabetic retinopathy has not been clarified.[2,7]

20.4 Frequency of screening

Screening should be performed at least annually.[2,4] If diabetic retinopathy is not present, the patient can continue to be screened annually.[2] However, if there are signs of diabetic retinopathy, he or she should be referred immediately to an ophthalmologist.[2,4]

20.5 Referral to an ophthalmologist

Patients with diabetes should be referred to an ophthalmologist when:

- A decrease in visual acuity is reported and/or confirmed, and there is no evidence of diabetic retinopathy. The patient should be referred within one month.[2]
- Only background changes are observed. The patient should be referred within one month.[2]
- Neovascularisation is present or suspected. The patient should be referred immediately.[2]

20.6 Management of diabetic retinopathy

- Evaluate the glycaemic, blood pressure and lipid control, and adjust treatment to reach targets recommended by guidelines.[2] Refer to an endocrinologist if targets are not met.
- Screen for other complications of diabetes.[2]

- Persons with sight-threatening retinopathy should be assessed by an ophthalmologist for laser therapy and/or vitrectomy and/or pharmacological intervention.[2]
- Visually disabled people should be referred to an optometrist for low-vision evaluation and rehabilitation.[2]

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21. Guidelines for the prevention and treatment of foot problems in diabetes

This section aims to highlight the morbidity and mortality associated with distal peripheral sensory diabetic neuropathy and its sequelae, and the measures that can be undertaken to prevent these. The epidemiology, risk factors, pathophysiology, prevention strategies and management of patients with neuropathy, nonulcerative pathology and ulcerated feet is discussed. Ulceration and amputation are preventable complications, and the healthcare provider should implement the measures outlined here in order to ensure optimal patient outcomes.

This guideline is adapted with permission from the Canadian Diabetes Association Clinical Practice Guidelines (2008), but includes input from the authors as well as the National Department of Health.

JEMDSA 2012;17(2):S69-S75

21.1 Defining the problem[1]

Foot problems are a major cause of morbidity and mortality in people with diabetes, and contribute to increased healthcare costs.[2,3] The sequence of events leading to lower-extremity amputation is well known. In people with neuropathy[4] and/or peripheral artery disease (PAD),[5] minor trauma to the foot leads to skin ulceration, infection and ultimately gangrene, resulting in amputation .[6-10] Foot complications are the major reason for admission to hospital of people with diabetes, accounting for approximately 20% of all diabetes-related admissions in the North American population;[8,9,11-13] unfortunately, no such data exist for the South African population. After amputation of one limb, the prognosis for the contralateral limb is poor .[14,15]

21.2 Risk factors for ulceration[1,16,17]

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

- Previous ulceration
- Neuropathy
- Structural deformity and limited joint mobility
- Peripheral vascular disease
- Microvascular complications (i.e. retinopathy, nephropathy).

21.3 Understanding how ulcers develop[18]

A crucial component of the pathogenesis of foot ulceration is most often peripheral sensory neuropathy.[19] This is present, to some degree, in more than 50% of people with diabetes who are older than 60 years.[20] Peripheral neuropathy must usually be profound before leading to loss of the protective sensation; the consequent vulnerability to physical and thermal trauma increases the risk of foot ulceration sevenfold.[21,22]

A second causative factor in foot ulceration is excessive plantar pressure.[23] This is related to both limited joint mobility (at the ankle, subtalar and first metatarsophalangeal joints) and foot deformities.[24-26] 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.[27]

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).[28] Those who had had a previous foot ulceration could withstand fewer cycles of stress to their feet before an ulcer recurred.[29]

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.[30,31]

21.4 Prevention of foot ulceration and amputation

A foot examination should form part of the annual review of patients with diabetes. Healthcare professionals trained in the assessment of feet should examine the patient's feet in order to detect risk factors for ulceration.

The informal carers of the person with diabetes should be advised by the healthcare professional on appropriate foot care.[32] Effective foot care involves a partnership between patients, carers and health professionals, and all decisions should be agreed upon by all these parties.

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.

An appropriate management plan for foot complications should include the promotion of beneficial self-care, ongoing foot-care education (Appendix A) and appropriated referral to specialists (e.g. podiatrist, vascular unit, orthotist, surgeon, wound-care unit).

Different patient education approaches should be applied to promote improved foot health 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.

21.4.1 General prevention strategies

- Optimal treatment of elevated blood glucose, blood pressure (BP) and cholesterol is crucial, as is smoking cessation.
- Regular inspection and examination of the shoes and feet should be undertaken at least annually, in order to identify the foot at risk.
- The patient, family and healthcare provider should be educated about foot care, including the use of appropriate footwear.
- Non-ulcerative and ulcerative foot pathology should be treated.

21.4.2 Regular inspection of the shoes

The patient should wear good shoes that fit well, and should 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.

Slip-on shoes and slippers are not recommended.

21.4.3 Regular examination of the feet

This includes assessment of the skin, bones, nerves and vasculature of the feet (Appendix B).

21.4.3.1 Skin

It is important to look for ulcers, scars from previous ulcers, corns, calluses, fissures, fungal infections, blisters and signs of trauma. Callus below the feet (i.e. plantar surface) over the metatarsal heads is important, as this indicates high plantar pressure.

The foot examination should also include a skin temperature assessment. 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.[32-34] This condition typically results in bony changes, and/or fractures, subluxations and dislocations. In addition, an acute Charcot foot may be associated with erythema and swelling, with overall clinical characteristics very similar to cellulitis.It may be necessary to distinguish an acute Charcot foot from osteomyelitis, particularly if ulceration is present.[35,36]

21.4.3.2 Bone

Deformities or prominent bony surfaces, claw or hammer toes, bunions, or the features of a Charcot foot should be noted.

21.4.3.3 Nerves

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 (Appendix C). The monofilament test is aimed at detecting neuropathy, not at identifying sites at risk of ulceration. If neuropathy is detected, plantar sites should be tested, for example the plantar surfaces of the first, third and fifth metatarsal and the distal plantar surface of the first toe as examples. A neurothesiometer can be used in a specialised setting.

If this equipment is not available, a cottonwool 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. Neuropathy is defined as two or more insensate sites out of the six.[37]

21.4.3.4 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. However, the atypical presentation of "ischaemia without symptoms" can manifest in patients with diabetes.

21.4.4 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).

Patients identified as being at moderate or high risk (category 1 and 2) of ulceration must receive intensive education focussing on prevention, and also routine treatment of nonulcerative foot pathology by a podiatrist. A healthcare professional must inspect their feet at every visit.

Table I. Risk categorisation system for diabetic feet[38,39]

Category	Risk profile	Follow-up frequency
0	No sensory neuropathy and no PAD	Once a year
1	Sensory neuropathy present, but no foot deformity or PAD	Once every six months
2	Sensory neuropathy and signs of foot deformity and PAD present	Once every three months
3	Previous ulceration or amputation	Once every one to three months

21.5 Specific management of positive findings on the foot examination

21.5.1 Painless neuropathy with loss of protective sensation

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

21.5.2 Painful peripheral neuropathy

The American Academy of Neurology (AAN) performed a systematic review and published guidelines for the treatment of painful diabetic neuropathy in 2011.[40] The following observations were made:

- Pregabalin (300-600 mg daily) was regarded as effective.
- A number of treatments were regarded as probably effective:
  - Gabapentin (900-3 600 mg daily)
  - Sodium valproate (500-1 200 mg daily)
  - Amitriptyline (25-100 mg daily); avoid in the elderly and those with cardiovascular disease, orthostatic hypotension and prostatism
  - Duloxetine (60-120 mg daily)
  - Venlafaxine (75-225 mg daily)
  - Dextromethorphan (400 mg daily)
  - Morphine sulphate (titrated to 120 mg daily)
  - Oxycodone (mean 37 mg daily, maximum 120 mg daily)
  - Tramadol (210 mg daily)
  - Capsaicin (0.075% four times daily)
  - Isosorbide dinitrate spray
  - Percutaneous electrical nerve stimulation for three to four weeks.
- The lidocaine patch was regarded as possibly effective.
- Treatments regarded as probably not effective by the AAN were oxcarbazepine, lamotrigine, lacosamide, clonidine, pentoxifylline, mexiletine, magnetic field treatment, low-intensity laser therapy, and Reiki therapy.

If the patient still has severe symptoms, in spite of a trial of a minimum of 14 days of amitriptyline or sodium valproate, 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.

21.5.3 Nonulcerative foot pathology

21.5.3.1 Pathology requiring podiatric or orthopaedic care.

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

21.5.3.2 Suspected peripheral artery disease.

If both pedal pulses are absent in either foot, with or without symptoms of chronic ischaemia, 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 the patient has a foot ulcer with at least one absent foot pulse (dorsalis pedis or tibialis posterior), he or she should undergo a full vascular assessment (i.e. Doppler studies).

In the interim, the cardiovascular risk management should be optimised: BP < 130/85 mm Hg; statin therapy at a higher dose, or low-density lipoprotein (LDL) cholesterol < 1.8 mmol/l if able to monitor and adjust statin therapy; 150 mg aspirin daily; and lifestyle modification, such as cessation of smoking, exercise and weight loss.

21.5.4 Ulcerative foot pathology

These patients should be referred to a diabetes or foot clinic at secondary- or tertiary-care level. The management principles are summarised below.

21.5.4.1 Management of diabetic foot ulcers[41]

1. Determine the cause (e.g. ill-fitting shoes).
2. Perform clinical grading (e.g. University of Texas grading system):[42]
   a. A-D: no infection or ischaemia (A), infection (B), ischaemia (C), both (D).
   b. 0-III: epithelialized (0), superficial (I), penetrates to tendon or capsules (II), penetrates to bone or joint (III).
3. Ulcer treatment:
   a. Relief of pressure:
   Non-weight bearing is essential.
   Mechanical unloading.

b. Restoration of skin perfusion:
Arterial revascularisation procedures, if required.
Treat smoking, hypertension and dyslipidaemia.

c. Treatment of infection:
Superficial ulcer: Extensive (chemical or sharp) debridement with removal of all necrotic tissue, and oral antibiotics aimed at *Staphylococcus aureus* and streptococci. No topical antibiotics.
Deep (limb-threatening) infection: Surgical drainage as soon as possible (emergency referral), with removal of necrotic or poorly vascularised tissue, including infected bone. Revascularisation, if necessary. Broad-spectrum antibiotics intravenously, aimed at Gram-positive and –negative microorganisms, including anaerobes.

d. Metabolic control and treatment of co-morbidity:
Optimal diabetes control, with insulin, if necessary.
Treat oedema and malnutrition.

e. Local wound care:
Frequent wound inspection.
Frequent wound debridement.
Absorbent, nonadhesive, nonocclusive dressings.
Footbaths are contraindicated, as they induce maceration of the skin.

f. Instruction of patients and relatives:
Appropriate recognition and self-care, as well as reporting of signs and symptoms of worsening infection, such as fever, changes in local wound condition or hyperglycaemia.

g. Determining the cause and preventing recurrence:
Determine the cause, as ulceration is a recurrent condition.
Prevent ulceration on the contralateral foot and provide heel protection during bed rest.
Patient must be included in a comprehensive foot-care programme.

21.5.4.2 Foot infection and infected ulcers

1. Diagnosis: Diagnose wound infections clinically (recognising that the inflammatory response may be mitigated by diabetic complications), by the presence of purulent secretions or local evidence of inflammation, or occasionally systemic toxicity.
   Laboratory tests, including cultures, may suggest but not establish the presence of infection, with the exception of deep-bone cultures obtained under sterile conditions in suspected osteomyelitis.
2. Nonantimicrobial treatment:
   a. Consult a diabetic foot-care team or specialist, where available.
   b. Correct any metabolic derangements, optimise wound care and assess vascular status.
   c. Hospitalise patients with a severe infection, those needing multiple or complex diagnostic or surgical procedures, those with critical foot ischaemia, those needing intravenous therapy, and those who are unlikely to comply with therapy.
   d. In case of severe infection, consult appropriate specialists promptly for necessary invasive diagnostic and surgical procedures.
3. Antimicrobial therapy:
   a. General principles:
      i. Prescribe for all clinically infected wounds immediately, but not for uninfected wounds.
      ii. Select the narrowest spectrum therapy possible for mild or moderate infections.
      iii. Choose initial therapy based on most common pathogens and known local antibiotic sensitivity data.
      iv. Adjust (broaden or constrain) empiric therapy based on the culture results and clinical response to the initial regimen.
   b. Specific choices:
      i. Cover staphylococci and streptococci in almost all cases.
      ii. Broaden the spectrum, if necessary, based on the clinical picture, previous culture or current Gram-stained smear results.
      iii. Topical therapy for mild superficial infections has not been adequately studied; oral therapy is effective for most mild to moderate infections; parenteral therapy (at least initially) is advisable for severe infections.
      iv. Choose agents that have demonstrated efficacy in treating complicated skin and soft tissue infections. These include semi-synthetic penicillins, cephalosporins, penicillin-β-lactamase inhibitors, clindamycin, fluoroquinolones, carbapenems and oxazolidinones.
      v. Treat soft tissue infections for one to two weeks if mild, and about two to four weeks for most that are moderate and severe. When the clinical evidence of infection has resolved, antibiotic therapy can be stopped.
4. Therapy of osteomyelitis:
   a. Consider surgically removing any infected or necrotic bone, if possible, and send for microbiology and culture and histology.
   b. Unless all infected bone is resected, provide antibiotic treatment (with parenteral therapy, at least initially) for at least four weeks.
   c. Treating for several months with highly bioavailable oral agents (especially fluoroquinolones) without surgical resection may be effective in selected patients.

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Appendix A

General principles for foot care (patient education)

- Wash the feet daily, using lukewarm water and soft soap.
- Inspect the feet daily, including the areas between the toes.
- Dry the feet gently, especially between the toes.
- Wear clean cotton or wool socks or stockings that are changed every day.
- Lubricating oils and creams should be used for dry skin, but not between the toes.
- Inspect or ask somebody to inspect the feet once a week, checking for redness, blisters, moist skin or cracks between the toes, cuts or scratches on the rest of the feet, and damaged nails.
- Cut the toenails straight across and not too short. Never cut down the corners of the toenails, as this may cause ingrown toenails. If the toenails cannot be cut, file them downwards. If your vision is impaired, ask someone to do this for you.
- Sharp instruments must never be used to dig around the toenails.
- Never 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.
- Avoid any clothes which restrict the blood flow to your feet. Never wear garters or socks with tight elastic tops.
- Stop or reduce smoking, as this adversely affects circulation.
- During cold weather, always remove all heating mechanisms (e.g. electric blanket, hot water bottle) from the bed before getting in.
- Remember to test the temperature of bath water before getting in. If you are unable to do so, let someone else test it. Avoid bathing in very hot water.
- The correct footwear is very important for the older person. It is bad for your feet and posture to wear slippers all day.
- Persons with diabetes should never walk barefoot when outdoors.
- Report every injury, blister, cut, scratch or sore that develops to the healthcare professional.
- Have the feet examined at least once a year by a healthcare professional.
- Look in shoes or feel inside them for hidden objects before putting them on.
- To avoid unnecessary foot irritation, do not wear worn-out shoes, socks or stockings. Socks must be worn with the seams on the outside.
- In general, shoes should suit the activity to be undertaken and follow the natural outline of the foot, fitting the widest part of the foot.
- 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.
- New shoes should be comfortable; there should be no need to "break them in".
- If special in-soles are needed, take them with you when buying shoes.
- The more you walk, the more your feet will swell; allow for this when buying shoes.
- Slip-on shoes are not recommended.
- Do not put on wet shoes.
- Air your shoes every day, even at night while you sleep or during the day when you rest.

Appendix B

Foot screening assessment form

Patient name	Hospital/clinic number	
Deformities or bony prominences	Yes	No
Skin not intact (ulcer)	Yes	No
Plantar callus	Yes	No
Monofilament neuropathy	**Left big toe (4 x)**	/ 4
	Right big toe (4 x)	/ 4
	Total	/ 8
Monofilament neuropathy if score < 7/8	Yes	No
Tuning fork neuropathy	**Left big toe (on 2 x, off 2 x)**	/ 4
	Right big toe (on 2 x, off 2 x)	/ 4
	Total	/ 8

Patient name	Hospital/clinic number	
Tuning fork neuropathy if score < 7/8	Yes	No
Light touch	**3 spots on each foot**	/ 6
Light touch neuropathy if score < 5/6	Yes	No
Dorsalis pedis pulse left present	Yes	No
Dorsalis pedis pulse right present	Yes	No
Tibialis posterior pulse left present	Yes	No
Tibialis posterior pulse right present	Yes	No
Peripheral vascular disease if both or both pulses absent on a foot	Yes	No
Previous ulcer	Yes	No
Previous amputation	Yes	No
Inappropriate footwear	Yes	No

Risk categorisation system for diabetic feet

Category	Risk profile	Follow-up frequency
0	No sensory neuropathy and no PAD	Once a year
1	Sensory neuropathy present, but no foot deformity or PAD	Once every six months
2	Sensory neuropathy and signs of foot deformity and PAD present	Once every three months
3	Previous ulceration or amputation	Once every one to three months

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Appendix C

Rapid screening for diabetic neuropathy

(Taken, with permission, from the Canadian Diabetes Association Clinical Practice Guidelines 2008.)[1]

Multiple screening methods for diabetic neuropathy have been published. These are designed to determine the presence or absence of diabetic neuropathy, as opposed to screening for specific sites on the feet that are at risk of ulceration (i.e. multi-site testing). If neuropathy is identified with the use of either the 10g Semmes Weinstein monofilament or the 128 Hz vibration tuning fork discussed here, other sites may be tested to identify high-risk areas for ulceration.

Rapid screening for diabetic neuropathy using the 10 g 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.
5. Use a smooth motion: touch the skin, bend the filament for a full second, and then lift it from the skin.
6. Perform this stimulus four times per 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.

Rapid screening for diabetic neuropathy using the 128 Hz vibration tuning fork ("on-off method")

1. Strike the tuning fork against the palm of your hand, hard enough so 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 stops, 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.

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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.

22. Diabetes care 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 type 2 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.

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22.1 Risks associated with uncontrolled diabetes in pregnancy

Uncontrolled diabetes mellitus (diabetes) during pregnancy poses numerous risks, for both mother and foetus. For example, mothers are more prone to hypertension, the development of hydramnios, and urinary tract infections. There is an increased risk of miscarriage, stillbirths and macrosomia, and higher rates of perinatal morbidity and mortality.

However, the outcome has improved considerably in many countries in recent years as a result of improved management, so that most women with diabetes in pregnancy can now expect a successful outcome.

22.2 Inheritance of diabetes

The risk of developing diabetes in offspring of diabetic parents is illustrated in Table I.

Table I. Risk of developing diabetes in the offspring of diabetic parents

Parent with diabetes	Type 1 diabetes	Type 2 diabetes
Father with diabetes	8-9%	15%
Mother with diabetes	2-3%	15%
Both parents with diabetes	≤ 30%	≤ 75%

22.3 Types of diabetes in pregnancy

- Gestational diabetes (GDM): Diabetes first diagnosed during pregnancy.
- Pregestational diabetes: Type 1 or type 2 diabetes diagnosed before the pregnancy, with or without complications of diabetes.

22.4 Diagnosis of GDM

Pregnant women with the risk factors listed below should undergo a two-hour 75 g oral glucose-tolerance test (OGTT) at booking and at 24-28 weeks' gestation to screen for GDM:

- 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-birthweight infant ≥ 4.5 kg
- Obesity [body mass index (BMI) > 30 kg/m^2]
- Women of South-Asian descent.

Women who were previously diagnosed with GDM should have an OGTT at 16-18 weeks and a further OGTT at 28 weeks if the results are normal.

22.4.1 Current criteria for diagnosis (World Health Organization)

These criteria will be revised in the near future:

- Fasting plasma glucose (FPG) ≥ 7.0 mmol/l; or
- Two hours post-glucose load (75 g) plasma glucose ≥ 7.8 mmol/L

22.4.2 Proposed criteria for diagnosis

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

- FPG ≥ 5.1 mmol/l
- One hour post-glucose load (75 g) plasma glucose ≥ 10.0 mmol/l

- Two hours post-glucose load (75 g) plasma glucose ≥ 8.5 mmol/l

22.5 Management of GDM

Pregnancy should ideally be planned in the patient with diabetes. Excellent glycaemic control [glycated haemoglobin ($HbA1_c$) < 7%) should be achieved for at least three months prior to conception, in order to minimise the incidence of congenital anomalies. Pre-conception assessment for diabetic complications (e.g. retinal, renal) should be performed, and managed accordingly.

All women with diabetes who are planning a pregnancy should be given dietary advice. Women with a BMI > 27 kg/m^2 should be offered advice on weight loss.

Folate (5 mg/day) should be taken just prior to conception and in the first 12 weeks of gestation to prevent neural tube defects.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II-receptor blockers (ARBs), diuretics and statins should be discontinued before conception, or as soon as pregnancy is confirmed.

Patients must be followed up every two weeks until 32 weeks of gestation, and weekly thereafter until just before delivery.

Frequent self-monitoring of capillary blood glucose is must be performed in pregnancy at the following times: pre-meal, one hour postprandial, and late at night.

The management of the pregnant diabetic requires intensive specialist supervision. Hence, referral to a centre with a diabetes-obstetric healthcare team (including a physician, obstetrician, paediatrician, dietitian and diabetes nurse educator) would be ideal.

22.6 Dietary therapy during pregnancy

The diet should comprise approximately 60% carbohydrate (complex, low-glycaemic index, high fibre); 25% fat (at least 50% unsaturated); and 15% 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 exercise is recommended, for at least 30 minutes daily.

22.7 Insulin therapy during pregnancy

Insulin therapy is indicated in all patients with type 1 diabetes. Insulin therapy should be initiated in those with GDM or type 2 diabetes if the target blood glucose levels (Table II) are not met.

Table II. Target blood glucose levels during pregnancy

Fasting	3.5-5.9 mmol/l
One hour postprandial	< 7.8 mmol/l

Multiple injections of short- and longer-acting insulins are recommended, i.e. short-acting human insulin, short-acting insulin analogues and intermediate-acting human neutral protamine Hagedorn (NPH) insulin. Long-acting insulin analogues should be avoided.

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).

The oral hypoglycaemic agents, metformin and glibenclamide, may be used in selected patients with type 2 diabetes and GDM, provided the target blood glucose levels are met.

22.8 Monitoring during pregnancy

As per the referral hospital protocol.

22.9 Education

Education on all aspects of diabetes and its management before and during pregnancy should be provided by suitably trained educators. Pre-conception counselling is particularly important.

22.9.1 Pre-conception counselling

The following topics must be covered:

- Contraception: Effective contraception must be used until optimum HbA_{1c} levels are achieved.
- Optimising glucose control:
  - Pre-conception HbA_{1c} must be as close to the normal range as possible, without significant hypoglycaemia.
  - Four to seven home blood-glucose tests should be carried out daily; refer to targets above
  - 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 responsible alcohol use.
- Medications
  - Ensure folic acid supplements
  - Review other medication: avoid angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, statins and diuretics. Treat hypertension with methyldopa.
- Screen for and refer diabetic complications e.g. retinopathy, nephropathy and cardiac disease
- Screen for immunity to the rubella virus.
- Counsel on risks associated with pregnancy in individuals with diabetes and obesity:
  - Risks to the foetus: Miscarriage, malformation, stillbirth, neonatal death and macrosomia
  - Risks to the pregnancy: Pre-eclampsia, pre-term delivery, and Caesarean section
  - Risks of progression of diabetic complications
  - Educate about sick-day rules.
- Arrange referral to an obstetrician, physician or diabetes specialist and a midwife at a centre with diabetes expertise

22.10 Management during labour or Caesarean section

As per the referral hospital protocol.

22.11 Postpartum

Neonates should be assessed by a paediatrician.

Patients with GDM should undergo a 75 g OGTT at six weeks to check for postpartum persistence of glucose intolerance.

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

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

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23. Diagnosis and management of type 2 diabetes in children and adolescents

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

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23.1 Diagnosis in children and adolescents

The diagnostic criteria of diabetes mellitus (diabetes) in children and adolescents are based on blood glucose measurements and the presence or absence of characteristic symptoms; i.e. polyuria, polydipsia, blurred vision and weight loss, in association with glycosuria and, in some cases, ketonuria.

There are three methods of diagnosing diabetes in adolescents and children:

1. Oral glucose tolerance test (OGTT), using 1.75g/kg anhydrous glucose dissolved in water to a maximum of 75 g; post-challenge plasma glucose (two-hour OGTT) > 11.1 mmol/l.
2. Fasting plasma glucose (FPG) ≥ 7.0 mmol/l.
3. Symptoms of diabetes and a random plasma glucose ≥ 11.1 mmol/l.

Tests for autoantibodies [glutamate decarboxylase (GAD) and IA 2 antibodies] should be done in all patients with clinical type 2 diabetes who are younger than 18 years. If the antibody tests are positive, there will likely be an earlier need for insulin, and autoimmune disorders associated with type 1 diabetes should be excluded.

23.1 Screening for type 2 diabetes

There is little published evidence to justify systematic screening of asymptomatic children for type 2 diabetes outside the research setting. However, opportunistic testing should be considered in overweight patients [body mass index (BMI) ≥ 85th percentile for age and sex) who satisfy at least two of the following criteria:

- Family history of type 2 diabetes in first-degree or second-degree relative
- High-risk ethnicity
- Signs of insulin resistance or conditions associated with insulin resistance (e.g. acanthosis nigricans, hypertension and dyslipidemia, polycystic ovary syndrome).

If the BMI > 99th percentile for age and sex, regardless of any additional factors, screening should be done.

Recommendations for screening:

- Initial screening may begin at 10 years of age or at the onset of puberty, whichever occurs earliest.
- Screening should be performed every two years.
- An FPG test is the preferred screening study.
- If the FPG does not meet diabetes diagnostic criteria, but clinical suspicion is high, a fasting OGTT is a more sensitive tool that can be utilised.

23.3 Management

The aim of management is to minimise the risk of the acute and chronic complications of diabetes through:

- Weight loss
- Increased exercise capacity
- Normalised blood glucose levels and glycated haemoglobin (HbA_{1c})(< 7%)
- Control of associated co-morbidities (e.g. hyperlipidaemia and hypertension).

If the patient presents in diabetic ketoacidosis (DKA) or the hyperglycaemic hyperosmolar state (HHS), immediate referral to a paediatrician is essential. There is a high risk of cerebral oedema and death in children and adolescents, and a paediatric protocol for the management of hyperglycaemic emergencies must be followed.

The best practice is to refer any patient with type 2 diabetes who is younger than 18 years to a paediatrician, or to at least discuss the case with a paediatrician if referral is not possible.

Diet and lifestyle modification, as well as medication, are important in the management of type 2 diabetes in children and adolescents.

If the patient presents with ketosis, acidosis and dehydration, treatment should be initiated with insulin. Metformin can be added later, once the patient is hydrated and ketone free. A low dose of metformin should be given at first (250 mg once daily); over the next three to four weeks, the dose can increase to 250 mg twice daily; then, the dose can be increased as it is tolerated and it can be guided by self-monitoring of blood glucose (SMBG) and HbA_{1c} results.

If there is doubt whether the diagnosis is type 1 or type 2 diabetes, treatment should be initiated with insulin and metformin, as described. Once the HbA_{1c} has been controlled, the insulin can be weaned. The patient should also be monitored for ketones.

In an otherwise well, less symptomatic child with the type 2 phenotype, metformin is the treatment of choice. Insulin therapy should be initiated if the HbA_{1c} is not controlled after six months.

Education of the patient, parents and caregivers is important. This should include training in SMBG. It must be emphasised that there is a possibility that the diagnosis could be type 1 diabetes, and that insulin may be required. SMBG is essential to prevent DKA and HHS.

Aspirin must not be prescribed for children and adolescents younger than 21 years.

23.4 Screening for complications and associated risk factors

Either micro- or macroalbuminuria may be present at diagnosis. Albuminuria should be evaluated at diagnosis, and annually thereafter. An angiotensin-converting enzyme (ACE) inhibitor is the first-line therapy. It is important to counsel girls and women of childbearing age about the teratogenicity associated with ACE inhibitors.

Hypertension (> 95th percentile for age, height and gender) may be present at or prior to diagnosis, and the blood pressure should be assessed at each visit, Hypertension is estimated to account for 35-75% of diabetes-related complications, both micro- and macrovascular. An ACE inhibitor is the first-line therapy, especially if microalbuminuria is present.

Dyslipidaemia is more common in individuals with type 2 diabetes and their family members than in the general population, and screening whould be done once metabolic stability has been achieved. Hypertriglyceridaemia and decreased high-density lipoprotein (HDL) cholesterol levels are hallmarks of type 2 diabetes-related dyslipidaemia. Weight loss, a low-cholesterol diet and improved glucose control are recommended. Statins are only to be used under specialist care, and with extreme caution in girlds and women of childbearing age.

Evaluation for non-alcoholic fatty disease (NAFLD), by assessing alanine transaminase (ALT), should be done at diagnosis and annually thereafter. Hepatic steatosis is present in 25-45% of adolescents with type 2 diabetes. This condition is the most common cause of cirrhosis in children, and the most common reason for liver transplantation in the adults in the US.

Dilated fundoscopy, to check for diabetic retinopathy, should be done at diagnosis and annually thereafter. Enquiry about puberty, menstrual irregularities and obstructive sleep apnoea should be made at diagnosis and regularly thereafter.

If any of these complications or risk factors are present, the patient should be referred to a paediatrician/ endocrinologist, or the case at least discussed with a specialist if this is not possible.

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24. Diabetes in older persons

The geriatric population has a high prevalence of diabetes mellitus. In 1993, 41% of 7.8 million people with diabetes were over 65 years of age. Many physiological changes with ageing affect the recognition, presentation and progression of diabetes in these individuals.

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24.1 Treatment goals in older persons

No significant increase in fasting plasma glucose (FPG) seems to occur with advancing age, but a small and significant increase in two-hour oral glucose-tolerance test (OGTT) plasma glucose has been noted. With age, the renal threshold for glucose rises, so glycosuria may not develop until the plasma glucose is markedly elevated. The same diagnostic criteria for diabetes mellitus (diabetes) and glycaemic, blood pressure (BP) and lipid targets apply in older as in younger persons.

In older individuals with impaired glucose tolerance, lifestyle interventions (moderate weight loss and regular physical activity) should be implemented to reduce the risk of type 2 diabetes. In the presence of multiple co-morbidities or a high level of functional dependence, goals should be less stringent (Table I).

Table I. Targets for control in older patients with diabetes

Parameter	Patients in good health	Frail older patients
FPG (mmol/l)	5.0–7.0	7.0–8.9
HbA_{1c} (%)[a]	6.5–7.5	7.5–8.5
BP (mmHg)	≤ 140/80	< 150/90

[a] Glycated haemoglobin

24.2 Precautions with drug therapy

24.2.1 Oral agents

Age is not a contraindication to metformin use, except if the serum creatinine is > 130 µmol/l. Regarding the sulphonylureas, glibenclamide should not be prescribed, as the risk of hypoglycemia increases exponentially with age. Gliclazide and glimepiride are preferred, and are associated with fewer hypoglycaemic and cardiovascular events. The meglitinides have also been associated with a lower frequency of hypoglycaemia. The glitazones should be avoided in older persons, because of the increased risk of salt and water retention, cardiac failure and osteoporotic fractures. Alpha-glycosidase inhibitors are poorly tolerated, because of gastrointestinal side-effects. Dipeptidyl peptidase-4 (DPP-4) inhibitors carry no risk of hypoglycaemia and are weight neutral, and may be attractive in older persons. However, long-term safety has not been established.

24.2.2 Insulin

Insulin should be initiated at a moderate dose of 0.25–0.35 units/kg/day. It is important to assess the patient's physical and cognitive functioning, in order to judge whether he or she will be able to use an insulin pen, monitor blood glucose, and recognise and treat hypoglycaemia.

24.2.3 Glucagone-like peptide-1 agonists

Glucagone-like peptide-1 (GLP-1) therapies carry no risk of hypoglycaemia, and are associated weight loss. Post-marketing reports of acute pancreatitis and renal dysfunction have been noted. There are insufficient data regarding use in older persons.

24.2.4 Aspirin

The value of daily aspirin as secondary prevention is well established, and the absolute benefit has been shown to be greatest in those older than 65 years with diabetes or diastolic hypertension. Aspirin is recommended by the American Diabetes Association (ADA) and American Heart Association (AHA), if the 10-year cardiovascular risk is > 10% in men older than 50 years and women older than 60 years with one other cardiovascular risk factor

24.3 Recommendations

In the absence of renal or cardiac contraindications, metformin is the preferred initial therapy. A short-

acting sulphonylurea should be initiated if metformin is contraindicated. In patients with chronic kidney disease or intoleranct of sulphonylureas, a meglitinide or DPP-4 inhibitor should be considered. Statins are well tolerated and have been shown to be effective as primary and secondary prevention, to significantly reduce cardiovascular morbidity and mortality. Fibrate therapy is also well tolerated.

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25. Diabetes in high-risk ethnic populations

The prevalence of type 2 diabetes is not the same in the different population groups of South Africa. It also seems that the risk for the development of diabetic complications is not equal for the different population groups. This section will highlight differences in prevalence of type 2 diabetes and the risk for complications between different ethnic populations of South Africa.

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25.1 Prevalence of diabetes

South Africa has a diverse population, with 79.5% of people classified as black, 9% coloured, 9% white and 2.5% Indian/ Asian.[1] According to the 2011 mid-year estimates of Statistics South Africa,[1] the estimated total population of South Africa was 50.6 million. The overall prevalence of diabetes mellitus (diabetes) is estimated to be about 5.5% for people older than 30 years of age, according to a South African burden of disease study.[2] However, significant disparities exist between different population groups with regard to the prevalence of diabetes, with people of Asian/Indian descent having a significantly higher risk of 17.1% in comparison to 6.4% of urbanised black people and 6.2% of white and coloured people. People of Asian/Indian decent seem to be at risk from a younger age, about 10 years earlier than the other population groups. Another high-risk group seems to be coloured people, with a particularly high risk in the age group older than 60 years (25.3%); females in this group have a prevalence of 33.3%. A third high-risk group is urbanised black females older than 60 years (16.7%).[2]

It is apparent from South African anthropometric data that there is a correlation between obesity and diabetes among coloured and African females, which is a possible explanation for the high prevalence of diabetes in these population groups.3 The obesity prevalence in coloured women was 26.3% and in black women 31.8%, in comparison to the prevalence in White women of 21.1%.[3]

For people of Asian/Indian descent, a poor correlation between obesity and diabetes has been noted at the same body mass index (BMI) cut-off values applied to black, white and coloured people. For this reason, the World Health Organization recommends the use of lower BMI levels when managing Indian patients. A patient should be considered "at risk" at a BMI of 22-25 kg/m^2, and at higher risk ≥ 26 kg/m^2.[4] A smaller waist circumference (women ≥ 80 cm, men ≥ 90 cm) should also be used to determine risk.[5]

25.2 Ethnic differences in diabetes complications

The data regarding differences in risk for diabetic patients of different ethnic origins for microvascular complications are sparse. With regard to macrovascular complications, there is not enough information available to conclude which ethnic group is at a highest risk. Retinopathy seems to be more prevalent among black and Asian/ Indian ethnic groups,[6] and, from a study conducted by Motala et al in Durban, it appears that black patients have a higher risk of developing retinopathy than Indian patients. Indian patients, however, seem to have a higher risk of microalbuminuria.[7] The data regarding differences in risk for diabetic patients of different ethnic origins for microvascular complications are sparse. With regard to macrovascular complications, there is not enough information available to conclude which ethnic group is at a highest risk.

C. Recommendations

Individuals of Indian descent should be screened for type 2 diabetes at an earlier age, probably from 30 years, and more frequently than patients who belong to other ethnic groups. When assessing these patients, a lower threshold for BMI and waist circumference should be used.

All coloured individuals and black females should be screened for diabetes from the age of 40 years, particularly if the BMI is raised.

Healthcare providers dealing with high-risk groups should be aware of increased risk of type 2 diabetes, and should be vigilant for the development of micro- and macrovascular complications.

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26. HIV and diabetes

This section is aimed at assisting with identifying HIV-positive patients on highly active antiretroviral therapy who are at risk of developing diabetes mellitus. The diagnosis, monitoring and management of such patients is discussed.

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26.1 Chronic metabolic complications

Patients with human immunodeficiency virus (HIV) infection who are on highly active antiretroviral therapy (HAART) have a longer life expectancy than before, because of a decline in the acute manifestations of the disease. However, there is a definite increase in chronic metabolic complications, related partly to HIV itself, but mainly caused by iatrogenic factors, such as HAART. Some of these metabolic complications include dysglycaemia and insulin resistance, dyslipidaemia, lipodystrophy, and accelerated atherosclerosis.

In South Africa, with an estimated population of 50 million, there are approximately 5.6 million people living with HIV. This is the highest number in the world. Currently, 1.4 million people are enrolled in the government roll-out program of HAART, and this number is expected to increase exponentially now that the CD4 cut-off point for treatment has been increased to 350 cells/mm^3. The current estimate is that about 2.6% of patients have both diabetes mellitus (diabetes) and HIV, but this number is higher in patients on protease inhibitors. Some studies report that up to 10% of patients on HAART develop diabetes within four years.

26.2 Risk factors for development of diabetes in HIV

The usual risk factors for diabetes count in this population, but a number of HIV-related risk factors could also be responsible for the development of diabetes:

- HIV virus itself: viral load, CD4 count, and duration of disease
- Rapid weight gain after the catabolic phase
- Co-infection with hepatitis C
- Dyslipidaemia with lipotoxicity
- Lipodystrophy
- Iatrogenic factors.

While the classic risk factors for the development of diabetes are well known, it has been postulated that HIV itself, and especially fluctuating viral load levels, induces a chronic inflammatory state. This results in an increase in cytokines [e.g. tumour necrosis factor (TNF), C-reactive protein (CRP), leptin) and a decrease in adiponectin levels, which may induce insulin resistance.

During the catabolic phase of HIV, patients lose lean muscle weight but, when they gain weight again, it's mostly fat which replaces the lost tissue. This overwhelms the secretory capacity of the β cells, which leads to insulin resistance.

Hepatitis C has been identified as a nontraditional risk factor for developing type II diabetes. The virus is associated with insulin resistance mainly at the level of the liver, by increasing intrahepatic TNF and causing hepatic steatosis.

However, the most common factors causing dysglycaemia still remain iatrogenic. Both the drugs used to treat opportunistic diseases and the antiretroviral drugs are implicated.

Of the drugs used to treat opportunistic infection, pentamidine is the most important one associated with metabolic complications. Pentamidine is used to treat *Pneumocystis jirovecii* pneumonia (PCP) in patients who are allergic to trimethoprim-sulphamethoxazole, and it is directly toxic to β cells. An initial release of stored insulin leads to hypoglycaemia at first. Ultimately, β-cell destruction takes place and there is reduced β-cell mass, with resultant hyperglycaemia.

The effects of antiretroviral drugs will be discussed in more detail below.

The corticosteroids are another group of commonly prescribed drugs. These drugs cause peripheral insulin

resistance with resultant reduced glucose consumption, and also increase hepatic gluconeogenesis.

26.3 Antiretroviral drugs and the development of diabetes

Antiretroviral drugs are the major cause of the development of diabetes in patients with HIV. Five classes of antiretroviral drugs are currently available in South Africa:

1. Nucleoside reverse transcriptase inhibitors (NRTIs): stavudine, zidovudine, lamivudine, abacavir, didanosine, tenofovir, emtricitabine
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs): efavirenz, nevirapine, etravirine
3. Protease inhibitors (PIs): indinavir, ritonavir, lopinavir, saquinavir, atazanavir, darunavir
4. Entry inhibitors: enfuvirtide
5. Integrase inhibitors: raltegravir.

The NRTIs cause dysglycaemia, mainly by three mechanisms:

1. Mitochondrial toxicity: This is responsible for the lactic acidosis for which these drugs are notorious. Lactic acidosis, in turn, leads to increased adipocyte apoptosis, with a resultant reduction in fat-cell mass (lipoatrophy) and, therefore, an increase in insulin resistance. Stavudine and didanosine have most often been implicated but, as treatment guidelines are being updated, these drugs are being phased out. The newer NRTIs (e.g. abacavir) are metabolically neutral.
2. Lipodystrophy.
3. Pancreatitis.

NNRTIs, fusion inhibitors and integrase inhibitors are metabolically neutral.

PIs induce insulin resistance by:

1. Lipodystrophy
2. Impaired glucose transporter type 4 (GLUT 4) translocation
3. Reduced adipocyte differentiation, by inhibition of peroxisome proliferator-activated receptor γ (PPAR-γ).
4. Reduced insulin secretion
5. Dyslipidaemia with lipotoxicity (indirectly).

The exact mechanism of PI-induced lipodystrophy remains unknown, but some studies have reported that up to 83% of patients on a PI develop lipodystrophy, and 35% of those go to develop diabetes. It is important to note that not all PIs are the same. Older-generation PIs (e.g. indinavir, ritonavir, saquinavir, lopinavir) are mainly responsible for insulin resistance at therapeutic dosages. However, these drugs are now only being used in PI-boosted regimens, with the exception of lopinavir and ritonavir. The newer-generation PIs (e.g. atazanavir, darunavir) are considered metabolically neutral.

26.4 Screening, diagnosis and monitoring

26.4.1 Screening

Everybody with the risk factors discussed earlier should be screened. For the non-HIV population, the recommendations are to repeat screening every three years but, in HIV-positive patients with risk factors, the frequency should be every six months. Fasting plasma glucose is the preferred test.

26.4.2 Diagnosis

The same diagnostic criteria for diabetes apply for HIV-positive as for HIV-negative patients. The same can be said of diagnostic methods but, in HIV-positive patients, an oral glucose-tolerance test is the preferred method.

Glycated haemoglobin (HbA_{1c}) is not a recommended diagnostic test in HIV-positive patients, because of the effects of the virus on haemoglobin, co-morbid conditions, and the effects of some antiretroviral drugs (e.g. zidovudine suppresses the bone marrow).

26.4.3 Monitoring

The same guidelines for self-monitoring of blood glucose (SMBG) apply for HIV-positive as for HIV-negative patients. SMBG is largely dependent on the kind of treatment the patient is on (e.g. oral agents vs. insulin, basal insulin vs. multiple insulin injections)

HbA_{1c} is still regarded as the gold standard in terms of monitoring for long-term glycaemic control, but the patient's general health and medical history must be taken into consideration as well.

26.5 Glycaemic targets

The HbA_{1c} target is < 7% for the majority of patients, with the exception of those who are already terminally ill or have advanced HIV-associated nephropathy, where the risk of hypoglycaemia will be high. Glycaemic targets should, therefore, be individualised.

26.6 Management

26.6.1 General management

Once again, the same general measures apply in HIV-positive and HIV-negative patients. However, it is important to remember the following in the HIV positive:

- Exclude sexually transmitted infections and, if present, treat appropriately.
- Exclude opportunistic infections, particularly tuberculosis, and, if present, treat appropriately.
- Exclude hepatitis C and, if present, treat appropriately.
- Avoid the use of so-called "immune boosters".
- Advise against use of traditional medicines.
- Advise the patient to stop smoking; this includes the use of snuff.
- Encourage psychosocial support from particularly the family, particularly since the patient will now have been diagnosed with two chronic diseases, and exclude depression.
- Emphasise and re-emphasise the importance of compliance for both diseases.

26.6.2 Medical treatment

26.6.2.1 Treatment of diabetes

The general principles for the use of both oral antidiabetic drugs and insulin apply but, in the HIV-positive patient, the following are important:

Exclude HIV-associated nephropathy (HIVAN) before initiating metformin, because lactic acidosis can occur.

The gastrointestinal side-effects of metformin are increased in those with HIV enteropathy. Start at a very low dose and titrate up gradually.

Stavudine and didanosine are being discontinued but, in those who are still being treated with these drugs, do not prescribe metformin, because lactic acidosis can occur.

26.6.2.2 Treatment of HIV

Metabolically neutral antiretroviral drugs should be prescribed in patients who are at high risk of developing diabetes. These include abacavir, atazanavir, darunavir, tenofovir and emtricitabine.

Stavudine, didanosine, lopinavir, sequinavir and indinavir should be avoided.

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27. Management of diabetes during Ramadaan

Fasting during the holy month of Ramadaan constitutes one of the five fundamental pillars of Islam. Muslims abstain from food and drink from dawn (Suhur) to dusk (Iftaar).Despite the fact that those who are ill are exempted from this obligation, many Muslims with diabetes mellitus still wish to fast. It is increasingly important that medical professionals be aware of potential risks associated with fasting during Ramadaan, and with approaches to mitigate those risks.

This section outlines criteria that define which diabetics can safely fast during Ramadaan, emphasises the importance of planning and education before Ramadaan, and provides guidelines on adjustments that need to be made at a therapeutic level to minimise the risks associated with fasting during Ramadaan.

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27.1 Fasting during Ramadaan

Fasting during the holy month of Ramadaan constitutes one of the five fundamental pillars of Islam. Muslims abstain from food and drink from dawn *(Suhur)* to dusk *(Iftaar)*. Despite the fact that those who are ill are exempted from this obligation, many Muslims with diabetes mellitus (diabetes) still wish to fast.[1] Patients with diabetes that fast are at risk of hypoglycaemia, hyperglycaemia and dehydration. Those who plan to fast need to undergo an assessment of risk before Ramadaan, and must participate in a structured education programme addressing meal planning, physical activity, dosage and timing of medications, glucose monitoring and the recognition and management of untoward events, including hypoglycaemia.[2]

The following individuals with diabetes are permitted to fast:

- Well-controlled patients with type 2 diabetes being treated with insulin, a short-acting insulin secretagogue (glinide), or a sulphonylurea, or a combination oral or oral plus insulin treatment. These patients can fast, provided they consult a healthcare professional several months before Ramadaan and make the necessary changes to their therapy.
- Well-controlled patients being treated with dietary adjustment alone, monotherapy with metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, or thiazolidinediones, and who are otherwise healthy.

Fasting is contraindicated in idividuals with:

- Type 1 diabetes
- Severe and recurrent episodes of hypoglycaemia with unawareness
- Poor glycaemic control
- Ketoacidosis within the three months before Ramadaan
- Hyperosmolar hyperglycaemic state within the three months before Ramadaan
- Severe acute illness
- Occupations that require intense physical labour
- Co-morbidities, such as advanced macrovascular complications, renal insufficiency, cognitive dys-function, and uncontrolled epilepsy (particularly when precipitated by hypoglycaemia)
- Pregnant women

27.2 Approach to patients with type 2 diabetes planning to fast during Ramadaan[3]

The patients should be assessed two to four months before Ramadaan.[4]

27.2.1 Medical assessment

The healthcare provider should follow an individualised approach for each patient. The overall glycaemic control, blood pressure, lipid profile and renal function should be assessed. Body weight and body mass index should be measured and recorded. The diabetes medication regimens should be assessed, and the treatment of choice, timing and dosage adjustments should be communicated to the patient.

27.2.2 Ramadaan-focused education

Patients and carers should be educated on the effects of fasting on diabetes. Aspects addressed should include meal planning, appropriate levels of exercise and blood-glucose monitoring. They should also be taught how to recognise and manage acute complications (e.g. hypoglycaemia, hyperglycaemia, dehydration), and when it is appropriate to break the fast

27.2.3 Diet-controlled patients

- Split the daily calorie allowance over two to three smaller meals during the non-fasting interval.
- Eat complex carbohydrates (e.g. oatmeal, bran, brown rice) at *Suhur* (pre-dawn meal), and simple carbohydrates at *Iftaar* (sunset meal).
- Avoid foods with a high sugar and fat content.
- Ensure an adequate fluid intake during the non-fasting interval.

27.2.4 Oral hypoglycaemic agents

- Individualise the choice of treatment.
- DPP-4 inhibitors, rapid-acting insulin secretagogues and thiazolidinediones may be used at meal times without dose adjustments.
- Ensure an adequate fluid intake during the non-fasting interval.

27.2.4.1 Metformin

The daily doses should be modified as follows:

- Two thirds after *Iftaar*
- One third at *Suhur*

If the patient is taking modified-release metformin once daily, take dose should be taken after *Iftaar* rather than at *Suhur*.

27.2.4.2 Sulphonylureas

Consider the following dose adjustments:

- Reduce the morning dose if taking the drug twice daily. For example, change a twice-daily dose of gliclazide 80 mg to 80 mg at *Iftaar* and 40 mg at *Suhur*.
- Consider a timing adjustment. For example, if taking a once-daily dose, switch it to Iftaar.[5]
- Consider switching from glibenclamide to gliclazide, glimepiride or glinide.[6]

27.2.4.3 DPP-4 inhibitors

DPP-4 inhibitors are an alternative to sulphonylureas if the risk of hypoglycaemia is high.[7]

27.2.4.4 Thiazolidinediones

No adjustment of thiazolidinediones is necessary.[8]

27.2.4.5 Acarbose

The usual doses of acarbose can be taken during meals

27.2.4.6 Oral short-acting insulin secretagogues

The glinides (e.g. repaglinide) are short acting and can be taken twice daily, at *Suhur* and *Iftaar*.

27.2.5 Injectable agents (type 2 diabetes)

27.2.5.1 Insulin

Ideally, overnight intermediate-acting insulin should be injected, plus a rapid-acting insulin before meals. Adjustment to treatment will be necessary. For example, the insulin glargine dose may have to be reduced by 20%. In the case of pre-mixed insulin, the usual breakfast dose should be administered in the evening *(Iftaar)*, and 50-75% of the usual evening dose should be taken in the morning *(Suhur)*.[4] An alternative would be to use Mix 50/50® preparation in the evening instead of a biphasic (30/70 or 25/75) pre-mixed insulin in order to achieve better postprandial control.[9]

27.2.5.2 Glucagon–like peptide-1 agonists

If a glucagon-like peptide-1 (GLP-1) agonist is used in combination with a sulphonylurea, no adjustment of the GLP-1 agonist is necessary. The dose of the sulphonylurea will have to be reduced.[10]

27.3 Approach to patients with type 1 diabetes planning to fast during Ramadaan

Patients with type 1 diabetes constitute a very high-risk group, for whom fasting is not recommended. Notwithstanding medical advice to the contrary, many patients still choose to fast. The recommendations below may be extended to insulin-treated type 2 diabetes patients receiving multiple-dose injection therapy. Those who wish to fast must be well controlled.[11] Treatment options include the following:

- Reduction in total dose of insulin to 70 % of the patients usual dose, with 60 % given as basal insulin in the evening, and 40 % short-acting split between the two main meals.[12]
- Short-acting insulin analogues, such as insulin lispro, offer the advantage of lower two-hour postprandial glucose concentrations after *Iftaar,* and fewer hypoglycaemic events than regular human insulin.[13]
- Basal insulin should be reduced by 20%, and the dosage of short-acting insulin taken before *Suhur* and *Iftaar* can be calculated using carbohydrate

counting based on the quantity and quality (carbohydrate content) of the meal.[14]

- Insulin-pump therapy may provide greater safety than conventional insulin regimens used in Ramadaan, especially with respect to hypoglycaemia that necessitates breaking of the fast.[14]

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28. Prevention/delay of type 2 diabetes mellitus in high risk individuals

Type 2 diabetes mellitus is a noncommunicable disorder with a rapidly rising prevalence. Treatment has been a serious challenge and, despite the availability of numerous medications, control remains suboptimal. A practical approach to addressing the rising tide of diabetes is to shift our attention to prevention, or delaying its onset.

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28.1 Evidence on prevention of diabetes

Diabetes mellitus (diabetes) is a pandemic associated with significant morbidity and mortality. Early detection of those at risk for the development of diabetes, and early intervention strategies, can prevent the progression of diabetes and its associated complications. Materials must be developed that will help people understand their risks for pre-diabetes and what they can do to halt the progression to diabetes and even to prevent the condition, if possible.

Patients with high-risk "pre-diabetic" conditions like impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) have a 25-50% lifetime risk of developing type 2 diabetes, and should be targeted for primary prevention.[1,2] To this end, a number of well-designed intervention studies, using lifestyle (diet and exercise) or drug therapy, have been conducted.

The Finnish Diabetes Prevention Study (FDPS)[3] and the Chinese Da Qing Study[4] 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 the level of physical activity.

The FDPS established a precedent for effectively altering lifestyle in patients with a high risk for diabetes. It included 522 subjects diagnosed with IGT according to the 1999 World Health Organization (WHO) criteria [fasting plasma glucose (FPG) < 7.8 mmol/l; two hours post-glucose load: 7.8-11.1 mmol/l). The intensive lifestyle modification group showed a 58% relative risk reduction when compared to controls, and continued effects were seen as a result of lifestyle change.[3,5]

The Da Qing study was undertaken in some 33 community clinics in Da Qing, China. A total of 577 subjects with IGT were randomised to a control group, diet control group, exercise group, or a combination of diet and exercise group, and followed over six years. All the intervention groups showed a reduction in development of diabetes of 31-46%, as compared to the control group.[4]

A few other trials have been done using, in addition to behavioural modifications, pharmacological interventions, In order to delay the onset of diabetes. Notable examples include the US-based Diabetes Prevention Program (USDPP),[6,7] the Troglitazone in Prevention of Diabetes (TRIPOD) trial,[5,6,8,9] the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial,[10] the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM),[11] the Indian Diabetes Prevention Programme (Indian DPP),[12] and the Actos Now for Prevention of Diabetes (ACT NOW) trial.[13]

After 2.8 years, the DPP showed a 58% reduction in those randomised to intensive lifestyle modification [weight loss and maintenance ≥ 7%, physical activity of moderate intensity (≥ 150 minutes per week), and individualised and group therapy dealing with lifestyle changes], vs. a 39% reduction in the group undertaking standard lifestyle modification and being treated with metformin 850 mg twice daily, vs. the control group on placebo.[5-9]

The TRIPOD study in Hispanic women with gestational diabetes showed a reduction of 55% after 30 months, which was maintained for eight months after discontinuation of the study drug, because of liver toxicity. These women were then changed to the PIPOD (Pioglitazone In the Prevention of Diabetes) study, which maintained the gain and even seemed to show a regression in decline of β-cell function.[3,5,6,8,9]

In the STOP-NIDDM study, there was a 25% relative reduction of developing diabetes in those treated with acarbose vs. placebo after 3.3 years. However, 31% of patients in the acarbose arm withdrew, as a result of side-effects.[11]

The XENDOS (XENical in the prevention of Diabetes in Obese Subjects) trial showed a relative reduction of 37.3% in those treated with orlistat and lifestyle modifications vs. placebo, but the better reduction was in the IGT group, where the incidence of diabetes was reduced by 45% over four years.[14]

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) vs. ramipril and placebo after three years.[10]

In ACT NOW, there was a reduction in the risk of conversion to diabetes of 72% vs. placebo over 2.4 years, although there was a significant rate of weight gain and oedema.[13]

A study done with liraglutide, a long-acting glucagon-like peptide-1 (GLP-1) agonist, mainly looked at weight reduction over 20 weeks. But, there was a sub-study of improvement from pre-diabetic to normoglycaemic glucose levels. A reduction in the level of pre-diabetes of 84-96%, depending on the dosage used (1.8-3 mg/day), was demonstrated over 20 weeks. Further follow-up is planned.[15]

The results from the trials on the prevention of type 2 diabetes are summarised in Table I.

Study	Therapy	Relative risk reduction
FDPS	Diet and exercise	58%
Da Qing study	Diet Exercise Diet and exercise	31% 46% 42%
USDPP	Diet and exercise Metformin 850 mg twice daily	58% 31%
DREAM	Rosiglitazone, diet, exercise and ramipril	60%
STOP-NIDDM	Acarbose	25%
ACT NOW	Pioglitazone	81%
Indian DPP	Diet and exercise Metformin 250 mg twice daily Diet, exercise and metformin 250 mg twice daily	29% 26% 28%

A number of drugs look promising for the prevention of type 2 diabetes, with the three that stand out being metformin, pioglitazone and liraglutide. Unfortunately, pioglitazone is an expensive drug and its side-effects limit its use. In the ACT NOW study, the weight gain was only an average of 3.6 kg; the more the weight gain, the better the glycated haemoglobin (HbA_{1c}). There was also no increase in cardiovascular events in the study.[13]

It is really too early to speculate on the role that liraglutide will play in prevention. Theoretically, it could be a good option, because of the possible improvement in β-cell function. However, liraglutide is expensive and needs to be injected.

Metformin is recommended by the American Diabetes Association for use in patients who are grossly overweight [body mass index (BMI> 35 kg/m²) and younger than 60 years, and have a family history of diabetes and have hypertension, a poor lipid profile and an HbA_{1c} > 6%. The dosage suggested is 850 mg twice daily.[9]

28.2 Drugs for the prevention of diabetes

Both the FDPS and USDPP trials showed an almost 60% relative risk reduction for progression of IGT to type 2 diabetes, providing solid evidence for the recommendations for lifestyle (diet and exercise) modification.

A number of problems are associated with recommending drugs for the prevention of diabetes. For instance, how long should patients stay on the drugs? And, will drugs alter or reverse the disease in the longer term? The recommended therapies should be safe in the long term, be effective, be cheap, and show other health benefits (e.g. cardiac disease prevention).[16]

Unfortunately, none of the current drugs fulfil these criteria, so our mainstay of therapy still remains lifestyle intervention with diet and exercise. The drug therapy that does show equivalent or superior preventive potential is from the glitazones group.[10,17] However, in the light of their potential for causing adverse events, it would be inadvisable to use these drugs for prevention.

Metformin has shown preventive potential, although at lesser efficacy, about 25-30% (USDPP, Indian DPP).[18] In view of its relative safety and low cost, it could be considered for diabetes prevention, especially in high-risk IGT patients, such as those who have associated hypertension, hyperlipidaemia, underlying cardiovascular disease and previous gestational diabetes.

28.3 Recommendations

- There is merit in identifying pre diabetes and preventing its progression to diabetes. Prevention of type 2 diabetes is best achieved with lifestyle modification (exercise and diet). This includes adoption of a low-calorie, low-refined carbohydrate, low-saturated fat diet; regular physical activity, comprised of sustained, moderate-intensity exercise of a minimum of 150 minutes per week; and a 5-10% reduction in body weight.
- High-risk individuals include those with a family history of type 2 diabetes; high-risk ethnic groups (e.g. South African Indians); the obese (BMI > 35 kg/m^2; increased waist circumference of > 94 cm in men and > 80 cm in women); a history of gestational diabetes; at least one component of the metabolic syndrome; cardiovascular disease; the presence of polycystic ovarian syndrome; and those with IGT or IFG.
- Those with a IGT or IFG together with a high-risk profile, or those who fail to control with lifestyle modifications, could benefit from the addition of metformin.

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29. Diabetes mellitus and driving

Driving represents freedom, control and competence for many people, and enables most people to access the places where they need to go: work, family gatherings, social functions, and private and public facilities, institutions and services. For many people, driving is important economically. Some drive as part of their jobs or to get to and from work. In South Africa, alternative means of personal transport are often limited. The impact of diabetes mellitus and its complications on a patient's ability to drive is not well appreciated or researched.

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29.1 Effects of diabetes on ability to drive

The chronic complications of diabetes mellitus (diabetes), such as retinopathy, cataracts and stroke, may affect driving performance. Hypoglycaemia, due to insulin or insulin secretagogues, may result in transient cognitive dysfunction or loss of consciousness, which could impair driving ability. People with diabetes require medical evaluation to assess and document the presence and severity of chronic complications and short- and long-term glycaemic control, including the frequency and severity of hypoglycemia, in order to determine their suitability to drive.

29.2 Current licensing requirements in South Africa

The current legislation in the Road Traffic Act of 1996 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, 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 healthcare 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 potentially 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.

29.3 Risks of diabetes and driving

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 license. The current evidence has been recently reviewed in detail in position statements from the American and Canadian Diabetes Associations.[1,2] Distiller and Kramer's review and recommendations for the local South African situation, published in 1996, are still very much valid today.[3]

Overall, studies are inconsistent and there are 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 as a whole, i.e. without differentiating those with a significant risk from those with little or no risk, as compared with the general population ranges between 1.126 and 1.19, a 12–19% increased risk. Society tolerates much higher relative risks associated with a variety of other situations, such as sleep apnoea, the very young driver or 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.

The most significant subgroup of persons with diabetes for whom a greater degree of restrictions is often applied across the rest of the world is drivers managing their diabetes with insulin. Yet, when the 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 in which drivers with diabetes are involved appears to be a recent history of severe hypoglycemia, regardless of the type of diabetes or the treatment used.

29.4 Recommendations for the South African situation

29.4.1 General

Generally, 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 concrete evidence of actual risk.

Healthcare professionals should be knowledgeable and regularly discuss ways to reduce the risks of driving with their patients who have diabetes.

Persons with diabetes should take an active role in assessing their ability to drive and in obtaining information about the 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.

29.4.2 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 hypoglycaemic events or hypoglycaemic unawareness should consult with their healthcare providers to determine whether it is safe to drive and to target interventions to avoid further episodes.

29.4.3 Commercial vehicles

Although South African law does not offer specific guidance here, it would seem reasonable for physicians to give strong advice here. Ideally, however, the law should provide clear guidance for annual assessment and clear criteria for holding a commercial licence.

Candidates with diabetes who apply for commercial licences should have an initial full medical assessment, as well as an 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. The following standards should apply:

- There has not been any *severe* hypoglycaemic event (requiring assistance from another person) in the previous six months.
- The driver has full hypoglycaemic awareness.
- The driver must show adequate control of the condition by regular blood glucose monitoring, at least twice daily and at times relevant to driving.
- The driver must demonstrate an understanding of the risks of hypoglycaemia.
- There are no other potentially dangerous complications or co-morbidies 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).

29.5 Patient education

Ideally, drivers at risk of hypoglycaemia should measure their blood glucose level before and at least every four hours during long drives. They should not drive when their blood glucose is < 4.0 mmol/l.

Drivers should stop, test and and treat themselves as soon as hypoglycaemia and/or impaired driving is suspected. They should not drive for 45-60 minutes after effective treatment of non-severe hypoglycaemia (not requiring assistance).

Drivers with a history of severe hypoglycaemia during the last year, hypoglycaemic unawareness, a recent marked fall in glycated haemoglobin (HbA_{1c}) or HbA_{1c} in the normal range should be informed that they are at high risk of hypoglycaemia when driving, and should make efforts to minimise that risk, particularly by closely monitoring blood glucose. Employers should be informed of this risk.

References

1. ADA Position Statement. Diabetes and driving. Diabetes Care. 2012; 35(S1):S81-S86.
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3. Distiller LA, Kramer BD. Driving and diabetics on insulin therapy. S Afr Med J. 1996;86:1018-1020.