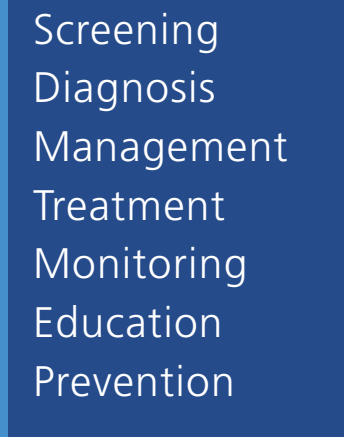




Fourth edition



Screening
Diagnosis
Management
Treatment
Monitoring
Education
Prevention

Type 2 Diabetes

Practical Targets and Treatments

Asian-Pacific Type 2 Diabetes Policy Group

Type 2 Diabetes

Practical Targets and Treatments

Fourth edition

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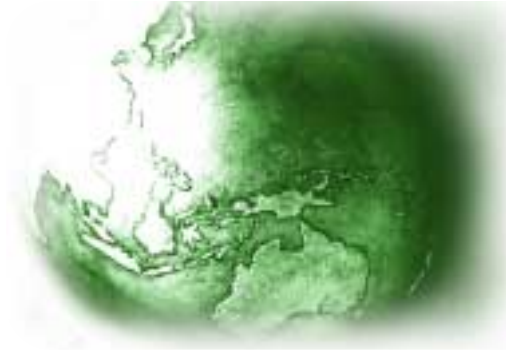
Supported by an educational grant from GlaxoSmithKline to the International Diabetes Federation (IDF) Western Pacific and International Diabetes Institute (IDI), a World Health Organization (WHO) Collaborating Centre for Diabetes.

Endorsed by the WHO Western Pacific Regional Office, IDF Western Pacific Region, Secretariat of the Pacific Community and Western Pacific Diabetes Declaration.

Asian-Pacific Type 2 Diabetes Policy Group

The Western Pacific Declaration on Diabetes

We, the World Health Organization Regional Office for the Western Pacific (WHO/WPRO), the International Diabetes Federation, Western Pacific Region, and the Secretariat of the Pacific Community, the signatories of this document, unite to highlight the serious nature of diabetes, currently estimated to affect at least 30 million people in the region. We, on behalf of people affected by diabetes, jointly call upon all governments, organisations and individuals in the region to undertake the following actions, according to the needs of each country:



1. Recognise the personal, public and economic burden of all types of diabetes and establish diabetes as a priority health concern.
2. Develop and implement national strategies and programmes to prevent and control diabetes, and reduce its risks.
3. Work towards universal access to quality care, training, essential diabetes medications, and other supplies and support for all people with diabetes.
4. Encourage a strategic alliance among governments, international and regional development agencies, health and non-health sectors, mass media, industrial partners, non-governmental organisations, and other stakeholders involved in the prevention and care of diabetes.
5. Recognise and promote the importance of education for people affected by diabetes, health professionals and the general public in the prevention and management of diabetes.
6. Integrate diabetes activities with those of other non-communicable diseases in order to promote healthy lifestyles and environments for the prevention and control of diabetes and its complications.
7. Recognise and address the problem of discrimination against people with diabetes.
8. Encourage research to advance and apply knowledge about the effective prevention, delivery of care and management of diabetes.



Foreword



The Asian-Pacific region continues to be at the forefront of the type 2 diabetes mellitus epidemic, with consequences to health which threaten to be devastating. Younger members of our communities are not spared from this disease, with a significant problem emerging in the urbanised young in more affluent parts of the region. Lifestyle changes and urbanisation appear to be the underlying causes of this problem, and continue to accelerate in this new millennium.

There is now overwhelming evidence of the need for optimal glycaemic control of type 2 diabetes if the impact of long-term microvascular complications is to be minimised. The UK Prospective Diabetes Survey has also highlighted the importance of both very good glycaemic control and good blood pressure control. This has been shown to be most relevant in the prevention of stroke and is, therefore, particularly important in this region where stroke is a significant cause of diabetes-related mortality.

Since publication of the third edition of *Type 2 Diabetes Practical Targets and Treatments*, new evidence has emerged relating to the prevention of both diabetes and its complications, as well as new International Diabetes Federation (IDF) reports on key issues in diabetes, including obesity, kidney disease and the metabolic syndrome. This fourth edition produced by the Asian-Pacific Type 2 Diabetes Policy Group is, therefore, timely. It provides an opportunity to update and revise those areas covered in the previous three editions, and to add new information in other areas, particularly with regard to the role of exercise, management of type 2 diabetes in children and adolescents, and management of other cardiovascular risk factors and the metabolic syndrome.

These guidelines have the support of the IDF, Western Pacific Region, and have been produced specifically with the needs of our region in mind. It should be emphasised that they are meant to complement rather than replace individual or national guidelines, to add the authority that can be provided by a regional approach as an additional support for national guidelines, and also to provide guidelines for those countries that do not have their own.

We recommend this booklet to you and sincerely hope that it will be used widely by a variety of healthcare professionals in all countries within the region.



A handwritten signature in black ink, reading "Pierre Lefebvre".

Pierre Lefebvre, President
International Diabetes Federation

A handwritten signature in black ink, reading "Martin Silink".

Martin Silink, President Elect
International Diabetes Federation

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Preface



The noncommunicable diseases (NCD) epidemic has overwhelmed the historical health problems of the Western Pacific region and is now the leading cause of mortality. Within the cluster of NCD, diabetes has become one of the most daunting causes of sickness and death. The current number of people with diabetes in the region is estimated to be 43 million and this number will increase to at least 76 million by the year 2025.

Studies carried out since the third edition of *Type 2 Diabetes Practical Targets and Treatments* indicate that the growth continues unabated. In Vietnam, the prevalence of diabetes doubled between 1994 and 2003. Cambodia has been shown to have figures comparable to provincial China. The Pacific Islands have remained at high levels or have increased.

However, the news is not all bad. There is irrefutable evidence that diabetes can be prevented or delayed in people at high risk, and that the progression of many of the complications associated with diabetes can be halted. Appropriate diet and physical activity, maintaining a healthy body weight, refraining from tobacco smoking, and proper control of diabetes and blood pressure in people with diabetes will help prevent diabetes and reduce its complications. The means to do this are within the reach of most countries' budgets. The issue is now not whether, but how, to deliver these solutions to the people of the region. Each country needs to develop appropriate guidelines for the prevention and control of diabetes, and set up systems to ensure that these guidelines are adhered to.

In some developing countries in the Western Pacific region, as many as three out of every four people with diabetes remain undiagnosed. When diagnosed, only about two thirds are undergoing optimal management (non-drug and drug), even in developed countries; and of those undergoing treatment, only one third are properly controlled.

In partnership with Member States and with the International Diabetes Federation, Western Pacific Region (IDF-WPR) and the Secretariat of the Pacific Community, the World Health Organization (WHO) supported the development of the Western Pacific Declaration on Diabetes in 2000, as well as its associated Plan of Action. As part of this collaboration, the WHO is supporting the development of customised clinical management guidelines for diabetes in Member States. This has now been achieved with WHO support in China, Mongolia, Vietnam and many Pacific Island countries and areas. We are observing significant initiatives in training (for example, The Philippines has produced a curriculum for primary health

workers that has been adopted nationwide). The Pacific Islands are also showing leadership (e.g. Fiji is running small opportunistic screening activities called mini-STEPS; the Cook Islands has set up a simple but effective spreadsheet-based audit tool for diabetes care). The region at large is working on the implementation of the Global Strategy on Diet, Physical Activity and Health and a number of development partners are supporting this essential development work. The prevention and control of diabetes is growing into a movement, with reassuring political commitment beginning to be expressed consistently across the region.

As an important resource in this work, I am pleased to present this fourth edition of *Type 2 Diabetes Practical Targets and Treatments*. This publication is a joint enterprise of the Type 2 Diabetes Policy Group, the IDF-WPR and the WHO Regional Office for the Western Pacific. I would like to thank the Policy Group, which has worked on the previous editions. This book will be a valuable tool for governments, the WHO, the IDF-WPR, the Secretariat of the Pacific Community, and other regional and national organisations, as we aggressively tackle this insidious disease with its propensity for striking at the many productive members of our society.



Shigeru Omi MD, PhD
Regional Director
WHO Regional Office for the Western Pacific

IDF-WPR Chairman's Statement



It is my great privilege to see a new edition of the International Diabetes Federation, Western Pacific region, *Type 2 Diabetes Practical Targets and Treatments*.

Diabetes is on the increase worldwide, especially in Western Pacific countries. In 1995, there were 135 million people with diabetes worldwide, with the number expected to rise to 330 million by 2025.

Most of this increase will occur in developing countries where an increase of 170% is expected, compared with an increase of 42% in the developed world. This indicates that over 60% of the world's diabetic population resides in the Western Pacific region. The living and eating habits of the people in our region are significantly different from those of Europe and elsewhere.

It is crucial to use medications according to people's needs, taking into account the vast differences extant in the region. I strongly believe that our differentiated guidelines provide for specific needs within the region.

As a diabetologist *and* a diabetic, I have no doubt that these guidelines will play a prominent role in reaching a recognised process of care and our own appropriate treatment goals.

Finally, I would like to acknowledge those individuals who contributed to writing this book, and to take this opportunity to express my gratitude for their generous contributions, which will also be appreciated by those who are fighting against diabetes.

A handwritten signature in black ink, appearing to read 'Sung-Koo Kang'. The signature is fluid and cursive, written on a white background.

Sung-Koo Kang, Chair
International Diabetes Federation, Western Pacific Region

Asian-Pacific Type 2 Diabetes Policy Group

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Chairmen's Statement



The number of people with diabetes worldwide is currently estimated to be about 190 million. By 2025, this number is expected to increase to over 330 million, with the majority of cases being type 2 diabetes.

Time Magazine has called diabetes "The Asian Disease".

The Asian-Pacific region holds one-third of the world's population, and includes a variety of ethnic groups. The type of diabetes in this region is predominantly type 2; however, significant pathophysiological differences exist when comparing type 2 diabetes in other ethnic groups with type 2 diabetes in Caucasians.

Following the publication of the European NIDDM Policy Group's *Desktop Guide for the Management of Non-insulin-dependent Diabetes Mellitus* in Europe, the Asian-Pacific NIDDM Policy Group met in 1994 with the aim of producing a document for this region. Information was obtained from all of the regional Diabetes Associations and from many key diabetologists. Our aim was to reach a consensus for all the countries involved; it was not an easy task to reach agreement but it was achieved. The goal was to target the treatment and prevention of type 2 diabetes and a first edition of *Type 2 Diabetes Practical Targets and Treatments* was published. This was updated in 1999 and 2002 as a result of new suggestions from the World Health Organization (WHO) and the American Diabetes Association (ADA) for diagnostic criteria and classification. Now, in 2005, with the availability of new medications and new data on the prevention of type 2 diabetes, and a new International Diabetes Federation (IDF) Consensus on a global definition for the metabolic syndrome, a newly revised version has become essential. A similar procedure to gain consensus has been followed, and we sincerely hope that this fourth edition will be an important and useful reference for clinicians and other health professionals involved in caring for people with diabetes.

Where evidence exists, which is not always the case in certain situations, the recommendations in this edition are evidence-based.

There is an increasing occurrence of type 2 diabetes in younger age groups than previously, and this issue has again been addressed in the current publication. We are fortunate to have the distinguished paediatrician, and incoming President of the IDF, Professor Martin Silink, provide a youthful perspective on the growing international problem of type 2 diabetes.

In addition, the Western Pacific Declaration on Diabetes 2000–2005 has been another welcome initiative that has helped set the stage for greater awareness of, and action on, type 2 diabetes in this region.

Finally, we would like to extend our sincere thanks to Dr Shigeru Omi, Regional Director of the WHO, Western Pacific Region, and Professor Kang, Chairman of the IDF, Western Pacific Region, for their active support and collaboration in assisting with the revised guidelines.



A handwritten signature in black ink that reads "Paul Zimmet". The letters are cursive and fluid.

Professor Paul Zimmet AO
Director, International Diabetes Institute
Melbourne, Australia

A handwritten signature in black ink that reads "Clive Cockram". The signature is stylized and cursive.

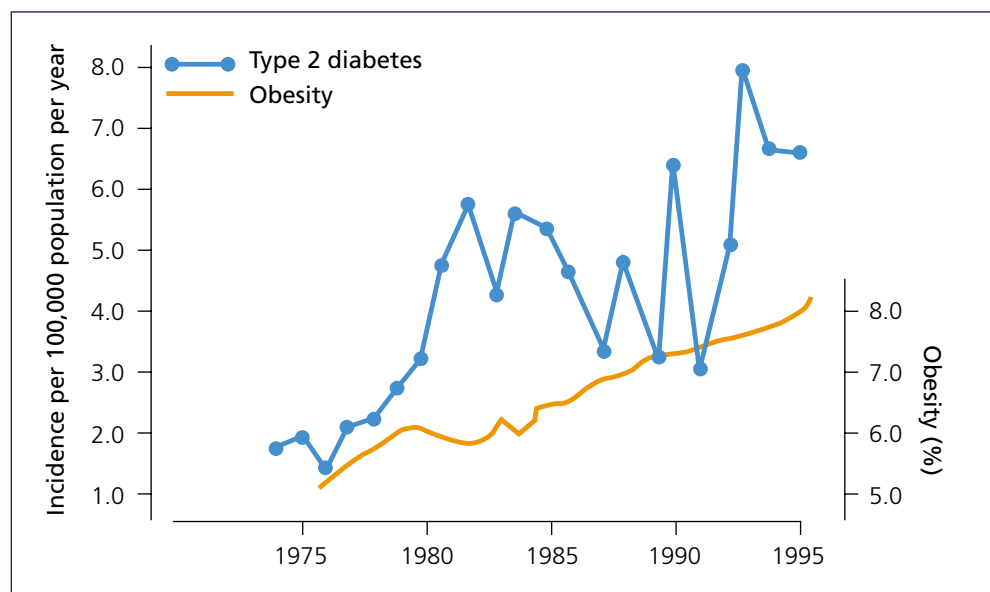
Professor Clive Cockram
Professor of Medicine
Chinese University, Hong Kong

The Price of Social Change

Type 2 diabetes is one of the major public health concerns in both developing and developed countries in the Asian-Pacific region. It has become epidemic in a number of countries, particularly in newly industrialised nations. The direct and indirect social and economic costs of treating diabetes and its complications have the potential to cripple the countries' healthcare budgets. In recent times, a new dimension has been added with the increasing appearance of type 2 diabetes in adolescents and even children (Figure 1).

FIGURE 1

Annual incidence of type 2 diabetes and prevalence of obesity among Japanese school children.¹



The prevalence of type 2 diabetes varies considerably across the region, from only 1% in Vietnam to 30% in Nauru (Figure 2).² Even within countries, major variations are seen. For example, Australian Aborigines have a diabetes prevalence 3–4 times that seen in the general (predominantly European – people of white European origin) Australian population, while some urban groups in Papua New Guinea have diabetes rates that are 10–15 times higher than their rural counterparts. Whilst the highest diabetes rates in the region are seen in Pacific Islanders and Australian Aborigines, each of the ethnic groups in the region have higher risks of type 2 diabetes than do Europeans. The extent to which this risk is expressed is strongly related to the degree of westernisation of lifestyle. Thus, in Nauru, type 2 diabetes went from being almost unknown to affecting 30% of adults over a period of about 50 years as lifestyle became westernised.

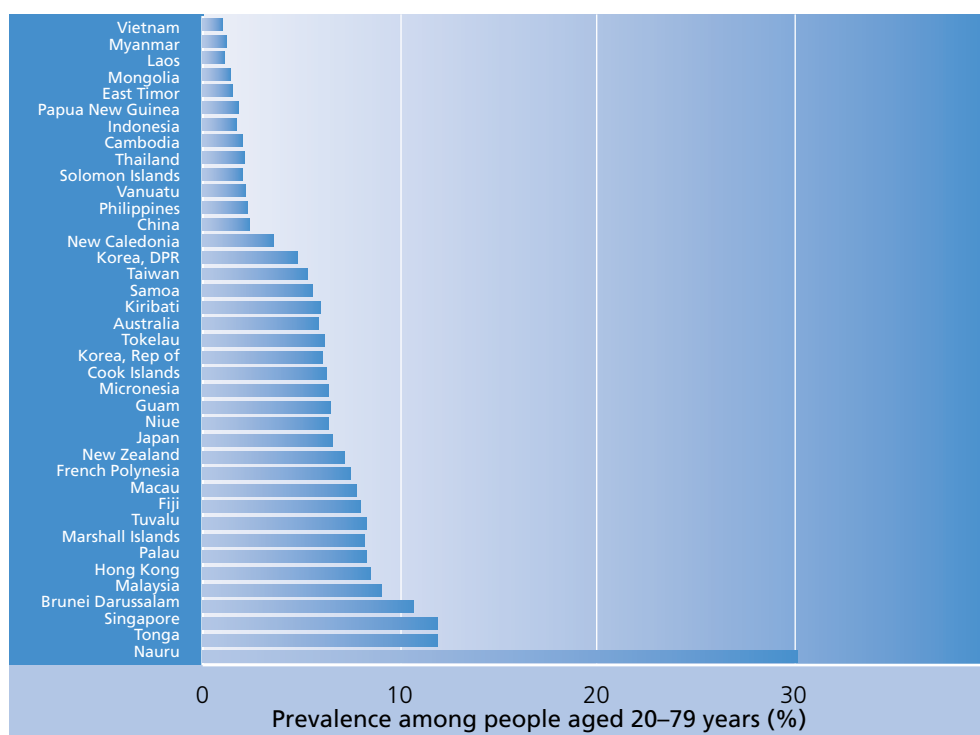


FIGURE 2

The prevalence of diabetes mellitus in adults in Asian-Pacific nations.²

Data taken from the *Diabetes Atlas*.²

Type 2 diabetes is a major cause of premature morbidity and mortality, particularly from cardiovascular disease (CVD), blindness, amputations and renal failure. In many instances, type 2 diabetes is seen clinically as part of the metabolic syndrome, a cluster of major CVD risk factors previously also referred to as the insulin resistance syndrome, Syndrome X or the Deadly Quartet.

Thus, the management of type 2 diabetes must address not only the control of hyperglycaemia but also the other CVD risk factors such as dyslipidaemia, hyperinsulinaemia, hypertension and obesity. Strategies for this approach are provided in this important consensus document.

The financial consequences of the burden of diabetes are significant, although data in the region are somewhat sparse. A study in China³ has estimated that for the urban population, the direct medical costs of diabetes are US\$451/year for someone without complications, rising to US\$1694/year for people with complications. In Australia, costs are much higher at US\$3012/year for those free of complications, US\$5277/year for those with microvascular complications, US\$6784/year for macrovascular complications, and US\$7256/year for those with micro- and macrovascular complications.⁴

Many of the complications of type 2 diabetes that contribute to the high cost of the disease, such as foot ulcers, are potentially preventable by good control of blood glucose, blood pressure and lipids.

Diagnosis Based on Venous Plasma

The diagnosis of diabetes is based on blood testing, which, wherever possible, should use venous samples, not capillary. Recently, the American Diabetes Association (ADA) re-examined the criteria for impaired fasting glycaemia (IFG)⁵ and recommended that the cut-point for IFG should be lowered to a fasting plasma glucose (FPG) ≥ 5.6 mmol/L (100 mg/dl). The change has been incorporated into this revised fourth edition. Please note that all values cited in this document refer to venous plasma glucose unless otherwise indicated.

TABLE 1
Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia.⁶

	Plasma venous glucose* mmol/L (mg/dl)
Diabetes mellitus:	
Fasting <i>and/or</i>	≥ 7.0 (126)
2-hour post-glucose load/casual	≥ 11.1 (200)
Impaired glucose tolerance (IGT):	
Fasting concentration (if measured) <i>and</i>	< 7.0 (126)
2-hour post-glucose load	7.8–11.0 (140–199)
Impaired fasting glycaemia (IFG):	
Fasting <i>and</i>	5.6–6.9 (100–125)
2-hours (if measured)	< 7.8 (140)

Note that a random (casual) plasma glucose cannot be used to diagnose IFG or IGT.

Modified from the WHO Consultation Report: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications*, 1999.

*Corresponding values for capillary plasma differ only for the 2-hour values: for diabetes mellitus, 2 hours ≥ 12.2 mmol/L (> 220 mg/dl); for IGT, 2 hours ≥ 8.9 mmol/L (≥ 160 mg/dl) and < 12.2 mmol/L (< 220 mg/dl).

For epidemiological or population screening purposes, the fasting or 2-hour value after 75 g oral glucose may be used alone. For clinical purposes, the diagnosis of diabetes should always be confirmed by repeating the test on another day unless there is unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms.

Indications for OGTT

Most screening programmes use either a fasting or a random glucose measurement as the first step. However, epidemiological studies have shown that with the current diagnostic thresholds, a significant proportion of people have isolated abnormalities of either the fasting or the post-load state. These people could, therefore, be incorrectly classified as normal by a single screening test, unless an oral glucose tolerance test (OGTT) is performed. In order to reduce the number of people who are missed in this way, it is recommended that an OGTT is performed on all people who have high normal fasting or random glucose values. Recent data suggest that an OGTT should be performed on all people with an FPG of 5.6–6.9 mmol/L, or a random plasma glucose of 5.6–11.0 mmol/L.

It is very important to emphasise that the HbA_{1c} value should not be used for the diagnosis of diabetes. Equally, the OGTT is not a test of diabetes control.

Type 1 or Type 2?

When taken in isolation, blood glucose levels are not useful for the classification of diabetes. Even ketoacidosis, which is often seen as the hallmark of type 1 diabetes, sometimes occurs in type 2 diabetes. Some experts may even have difficulty with the initial classification of a patient.

Classification can be particularly difficult in young adults, as type 1, type 2 and latent autoimmune diabetes in adults (LADA) may be equally common. LADA presents initially like type 2 diabetes, but will progress to insulin dependency within months or a few years. Although type 2 diabetes in Europeans is usually characterised by onset (often asymptomatic) after the age of 50 years, in Pacific Islanders and other high-prevalence groups, such as south and south-east Asians, onset in the 20–30-years age group is now increasingly common, and it is now seen in the pre-adolescent child.

If there is uncertainty in diagnosis, a provisional classification should be made and reassessed after an initial response to therapy.

Results from a number of studies, including the ASDIAB initiative,⁷ indicate that measurement of C-peptide and the antibodies to glutamic acid decarboxylase (anti-GAD) can be useful to assist in making the distinction.

Type 1 diabetes

- Generally < 30 years of age at presentation
- Moderate-to-severe symptoms
- Lean
- Low fasting or post-prandial C-peptide
- Rapid onset
- Significant weight loss
- Ketonuria or ketoacidosis
- Immune markers (anti-GAD, ICA, IA-2)

Type 2 Diabetes in Childhood and Adolescence



Type 2 diabetes has emerged recently as a problem among adolescents and young adults, particularly in high-prevalence populations.

Although type 1 diabetes remains the most prevalent form of the disease in children worldwide, it is likely that type 2 diabetes will be the predominant form within 10 years in many populations. Type 2 diabetes has already been reported in children from Japan, the Pacific Islands, Hong Kong, Singapore, China, Malaysia, Korea and Australia. Among children in Japan, it is already more common than type 1 diabetes, accounting for 80% of childhood diabetes; the incidence has almost doubled between 1976–80 and 1991–95.

	Type 1 diabetes	Type 2 diabetes
Onset	Acute – symptomatic	Slow – often asymptomatic
Clinical picture	<ul style="list-style-type: none"> • Weight loss • Polyuria • Polydipsia 	<ul style="list-style-type: none"> • Obese • Strong family history type 2 diabetes • Ethnicity – high-prevalence populations • <i>Acanthosis nigricans</i> • PCOS
Ketosis	Almost always present	Usually absent
C-peptide	Low/absent	Normal/elevated
Antibodies	<ul style="list-style-type: none"> • ICA positive • Anti-GAD positive • ICA 512 positive 	<ul style="list-style-type: none"> • ICA negative • Anti-GAD negative • ICA 512 negative
Therapy	Insulin invariably	Lifestyle, OHA or insulin
Associated auto-immune diseases	Yes	No

TABLE 2

Features to differentiate type 1 and 2 diabetes in young people.⁸

Adapted from Alberti *Diab Care*, 2004.⁸

PCOS – polycystic ovarian syndrome; ICA – islet cell antibodies; Anti-GAD – glutamic acid decarboxylase antibodies; OHA – oral hypoglycaemic agents.

The majority of patients with type 2 diabetes present insidiously, are obese, and have a strong family history of type 2 diabetes. A very small minority present more acutely with polyuria, polydipsia and ketosis, requiring transient initial insulin therapy. As a result of this new and rather alarming scenario, a joint consensus statement has been issued recently by the ADA and the American Academy of Pediatrics.⁹



FIGURE 3

Acanthosis nigricans. The darkening of skin around the neck is often a sign of insulin resistance.

McMahon SK *et al.* Increase in type 2 diabetes in children and adolescents in Western Australia. *MJA* 2004; 180: 459–61. © Copyright 2004. *The Medical Journal of Australia* – reproduced with permission.

Essentials of Management

The self-care programme

Team-based care and patient education



Diabetes is best managed by a team, which includes not only healthcare professionals, but also the patient. Evidence for extending the team beyond the physician comes from studies showing the benefits to patient outcomes of patient education and of interventions by nurses.¹⁰⁻¹³

The team-based approach allows flexibility in delivery of care, and improves communication between healthcare professionals. This may be particularly appropriate in rural settings, where access to physicians may be limited.

The standard core team is shown below, but may need to be tailored to local settings:

- Medical practitioner (general practitioner and/or specialist physician)
- Diabetes educator
- Dietician
- Patient

Additional members of the team can be added when necessary and might include ophthalmologists, cardiologists, nephrologists, vascular surgeons, obstetricians, podiatrists and psychologists.

Where facilities are available, the team-based approach should be complemented by a system of call and recall to ensure that all patients have regular assessments of metabolic control and complications. When such systems are computerised, they can also be used to provide evidence and guidelines on best practice, which can be available at the point of care to all healthcare professionals.

The patient with diabetes should know:

- The nature of the disorder.
- Symptoms of diabetes.
- Risk of complications and, in particular, the importance of foot care.
- Individual targets of treatment.

- Individual lifestyle requirements and meal planning.
- Importance of regular exercise in treatment.
- Interaction of food intake, physical activity and oral hypoglycaemic drugs, insulin (administration and adjustment of insulin, when appropriate) or other drugs.
- Self-monitoring of blood or urine glucose (only if blood glucose monitoring is not available or practical), and the meaning of blood glucose results, as well as what action needs to be taken.
- How to cope with emergencies such as illness, hypoglycaemia, stress and surgery.
- Women with existing diabetes require special attention during pregnancy.

Patient education has been shown to improve a range of outcomes, including metabolic control, and is essential for successful self-care.¹⁰⁻¹³ Therefore, a teaching programme must be offered to each patient.

Management is an active partnership between people with diabetes, their family and their healthcare team.

Other community resources are often available to supplement this.



Monitoring of Glycaemic Control

The gold standard for assessment of long-term glycaemic control is glycated haemoglobin (HbA_{1c}), and this should be measured every 3–6 months.

HbA_{1c} should be used as the prime determinant of success of glycaemic control, and of the need to change therapy if necessary. In a small proportion of people (mainly those with abnormalities of red cell turnover, such as haemoglobinopathies),

HbA_{1c} is unreliable. Where facilities for measuring HbA_{1c} are not available, a fasting blood glucose level is a reasonable alternative. In the absence of laboratory facilities, a finger-prick fasting capillary glucose can be used.

Self-monitoring of glucose levels

Monitoring of glucose levels can be done by either blood or urine testing. Blood testing is optimal; however, if this is not available, urine testing is an acceptable compromise. The frequency of monitoring will depend upon available resources, either to the individual or the country concerned.

Self-monitoring of blood glucose levels should be regarded as essential to improve the safety and quality of treatment for those who are treated with insulin, and during pregnancy. It is a vital safeguard against hypoglycaemia. Evidence is less clear for those not treated with insulin, as some,¹⁴ but not all, trials have shown a benefit in improving glycaemic control. Methods and frequency of self-monitoring depend on the targets and mode of treatment. Blood measurements should be recorded.

Self-monitoring

Self-monitoring technique should be checked once or twice per year by the physician or healthcare team. Quality control of tests is essential, particularly if results are inconsistent with HbA_{1c} or clinical state.

Extra tests should be performed during illness or prior to strenuous activity.

Urine ketone tests should be performed during illness or when blood glucose is > 20 mmol/L (> 360 mg/dl).

Monitoring procedures

Test:

- before each meal
- at bedtime
- 2-hours post-prandial (optional)

Monitor well-controlled/stable patients 1 or 2 days per week.

This can be less frequent in consistently well-controlled patients.

Monitor poorly controlled/unstable patients, or patients during illness, daily until targets of control are achieved.

Urine self-monitoring

Urine glucose self-monitoring is an alternative to blood glucose self-monitoring only when the latter is not possible. The aim generally is to keep the urine glucose-free. However, urine testing does not detect hypoglycaemia, and is not useful in certain situations such as where the renal threshold is elevated (e.g. in the elderly) or low (e.g. in pregnancy).

Blood glucose testing is the optimal self-monitoring method; however, in certain countries this is not available and urine testing is acceptable.

	HbA _{1c} (%)	FPG/pre-prandial PG	2-hour post-prandial PG
Target for most patients	≤ 6.5*	4.4–6.1 mmol/L (80–110 mg/dl)	4.4–8.0 mmol/L (80–145 mg/dl)

TABLE 3

Recommended targets for glycaemic control.

*Value applies to a DCCT-aligned assay.

FPG – fasting plasma glucose; PG – plasma glucose.

Treatment goals and strategies must be tailored to the patient, with consideration given to individual risk factors.

Food Planning



Effective management of type 2 diabetes cannot be achieved without proper attention to diet and nutrition. This extends to associated cardiovascular risk factors such as hypertension, dyslipidaemia and obesity.

Principles of nutrition^{15,16}

Nutrition is an integral part of the management of diabetes. The goals of nutritional management are to:

- achieve and maintain optimal blood glucose levels
- reduce cardiovascular risk factors, including dyslipidaemia and hypertension
- provide a balanced, nutritional diet.

Weight control

- A weight loss goal of 5–10% of body weight over 3–6 months is recommended for people who are overweight.
- Long-term maintenance of achieved weight loss and prevention of weight gain are important.
- Reduce total energy intake by reducing portion sizes and avoiding excessive intake of fats and sugar.

Fat

- *No more than 30% of total energy intake should come from fat.*
- Restrict saturated fat to less than 10% of total energy intake.
- Avoid or limit the following: fatty meats, full cream dairy products, palm oil, coconut oil and processed foods.
- Use mono- and polyunsaturated fats in place of saturated fat.

Carbohydrate

- *Carbohydrate should provide 50–55% of the total energy intake.*
- Meals should contain mostly carbohydrate with an emphasis on high-fibre foods such as vegetables, legumes, wholegrain cereals, yams and fruit.
- Sucrose should provide no more than 10% of total energy intake.
- Small amounts of sugar can be consumed as part of a healthy eating plan and non-nutritive sweeteners may be used to replace larger quantities of sugar, such as in soft drinks and confectionery.
- Eat three meals daily to distribute carbohydrate intake during the day.

Protein

- Protein should provide 15–20% of total energy intake.
- Good sources of protein are fish, seafood, lean meat, chicken, low-fat dairy products, nuts and legumes.

Alcohol

- Restrict alcohol intake to no more than 1–2 standard drinks/day.
A standard drink, for example, 285 ml beer, 375 ml light beer, 100 ml wine or 30 ml spirits, contains 10 g of alcohol.
- Alcohol may cause hypoglycaemia in patients on sulphonylureas or insulin.

Salt

- Restrict salt intake to less than 6 g/day, particularly in people with hypertension.
- Limit foods which are high in salt such as preserved and processed foods, and sauces (e.g. soy, oyster and fish sauces). Choose low-salt varieties of food where possible.

Eat most

Use one or more of these foods as the basis of every meal

Vegetables, legumes, lentils, noodles, rice, bread, grains, barley, wholegrain cereals, fresh fruit (non-sweet)

Note that many sauces and preservatives that are added to these foods are high in salt, sugar or fat, and should be avoided.

Eat moderately

Have small servings of protein-rich foods

e.g. fish, seafood, eggs, lean meat, skinless chicken, low-fat cheese, low-fat yoghurt, low-fat milk, nuts

Eat least

Minimise fats, sugars, salt and alcohol

e.g. butter, oil, ghee, cream, coconut milk and cream, processed meat, fried foods, preserved or processed foods, pastries, sweets, biscuits, soft drinks



Physical Activity

Physical activity plays an important role in the management of type 2 diabetes. Physical activity improves insulin sensitivity, thus improving glycaemic control, and may help with weight reduction.¹⁷ People with diabetes who undertake regular physical activity have been shown to have substantially lower mortality rates over 12–14 years.^{18,19}

The common health goal should be to achieve at least 150 minutes of moderate-intensity physical activity each week.¹⁷ This includes activities such as brisk walking, tai-chi, cycling, golf and gardening. Additional health benefits can be obtained by more vigorous activities (such as dancing, aerobics, jogging, lap-swimming, cycling uphill or heavy digging in the garden), or through longer durations of moderate-intensity activities. Strength-developing activities (e.g. strength-training) should be encouraged at least twice per week for the major muscle groups of the legs, trunk, arms and shoulders, with the emphasis on using light-to-moderate resistance, but performing more repetitions (8–12) on each physical activity.²⁰ Physical activity programmes need to be appropriate for the person's age, social, economic, cultural and physical status.



Do sparingly

Avoid sedentary activities

e.g. watching television, using the Internet, playing computer games

Do regularly

Participate in leisure-time physical activity and recreational sports

e.g. brisk walking, golf, strength-training, cycling, ball games

Do every day

Adopt healthy lifestyle habits

e.g. walk to the shops instead of driving,
use the stairs rather than the elevator,
walk to office colleagues instead of using
the telephone, walk the dog

Adoption of healthy lifestyle practices within daily living, such as taking the stairs rather than the elevator/escalator, or maximising opportunities for vigorous physical activities such as those that would have occurred with traditional lifestyles, should be encouraged. However, careful attention should be paid to potential physical activity hazards such as cuts, scratches and dehydration, and special care of the feet should be taken.

If physical activity is sudden and/or vigorous, people with diabetes should be advised about adjusting their food intake or medications (insulin or oral agents) in order to avoid hypoglycaemia.



Pharmacological Treatment of Hyperglycaemia

Drug treatment should be added only when diet, physical activity and education have not achieved individual treatment targets.



The pharmacological treatment of hyperglycaemia is based on the two key metabolic abnormalities in type 2 diabetes – insulin resistance and impaired insulin secretion. Thus, each hypoglycaemic agent targets one of these abnormalities, and combination therapy is often required to address both components. Sulphonylureas and glinides directly stimulate insulin secretion, while thiazolidinediones and metformin improve insulin sensitivity. α -glucosidase inhibitors slow down carbohydrate absorption, hence reducing the need for post-prandial insulin secretion.

If the patient is very symptomatic or has a very high blood glucose level, diet and lifestyle changes are unlikely to achieve target values. In this instance, pharmacological therapy should be started without delay.

Algorithms showing the treatment of obese and non-obese individuals can be found on pages 27 and 28.

Metformin

Metformin is recommended as first-line therapy in the obese and overweight, and is recommended as first-line therapy in non-obese patients in some countries. The UK Prospective Diabetes Study (UKPDS) has demonstrated that metformin is able to reduce HbA_{1c} as effectively as sulphonylureas and insulin without significant weight gain.²¹ Importantly, it is the only hypoglycaemic agent that has been shown to reduce CVD and mortality.²¹ Metformin does not cause hypoglycaemia or weight gain, but often leads to troublesome gastrointestinal side effects, which are frequently dose dependent, and can emerge after many years of treatment. In the USA, metformin has also been shown to prevent or delay progression from IGT to diabetes.²²

Note: Metformin must not be used in patients with impaired renal function, liver disease or septic shock, or during major surgery because of the risk of lactic acidosis. If the serum creatinine level is above 150 $\mu\text{mol/L}$ (1.7 mg/100 ml), metformin should not be used.

Sulphonylureas

Sulphonylureas stimulate insulin secretion by the beta cells, and lower HbA_{1c} by 1–2%. The UKPDS confirmed that they reduce the progression to microvascular complications by 25%.²³ However, they usually lead to weight gain, and can cause hypoglycaemia (particularly with chlorpropamide and glibenclamide), especially in the elderly, and in those with renal or liver disease. Thus, sulphonylureas should usually be used as second- or third-line agents.

Note: Gliquidone is the sulphonylurea of choice in renal impairment.

Thiazolidinediones

The thiazolidinediones, such as rosiglitazone and pioglitazone, improve insulin sensitivity, by improving cellular response to insulin action; however, they do not enhance insulin production. They decrease HbA_{1c} by approximately 1–2%, and do not cause hypoglycaemia. Weight gain is a common side effect, though it usually results from increased subcutaneous fat, rather than an accumulation of visceral fat. Fluid retention may occur, and in those with pre-existing heart disease, cardiac failure may be precipitated.

Thiazolidinediones should not be initiated in patients with active liver disease or transaminase levels above 2.5 times the upper limit of normal. Abnormal liver function tests have not been reported with rosiglitazone or pioglitazone; nevertheless, it is currently recommended that liver function be monitored periodically. In addition, weight increase and fluid retention may occur as a result of thiazolidinedione therapy.

Rosiglitazone and pioglitazone have shown some significant changes to surrogate markers for cardiac disease, suggesting a long-term beneficial effect, and outcome studies are currently under way to examine this, as well as their potential to prevent diabetes.

α-glucosidase inhibitors

α-glucosidase inhibitors, such as acarbose, miglitol and voglibose, slow down carbohydrate absorption from the jejunum, and hence decrease post-prandial blood glucose and, to a lesser degree, fasting glucose, thus improving overall glycaemic control. They have a weight-neutral or weight-reducing effect, and can be used as first-line therapy in association with diet, or in combination with sulphonylureas, metformin and insulin. These drugs may lower HbA_{1c} by about 1%.

Gastrointestinal side effects are common, and in order to minimise them, a low starting dose is recommended followed by a gradual increase.

In the STOP NIDDM study,²⁴ acarbose has been shown to prevent or delay progression from IGT to diabetes. There is also evidence to suggest that it may reduce the risk of developing CVD.

Glinides

A new generation of sulphonylurea-like agents has recently become available in several countries in the region. The compounds, which include nateglinide and repaglinide, appear to stimulate early insulin secretion. Glinides may be used as monotherapy or in combination therapy with biguanides or thiazolidinediones. They reduce post-prandial hyperglycaemia, and have to be taken with each meal.

Combination oral therapy

Metformin, sulphonylureas (or glinides), thiazolidinediones, and α -glucosidase inhibitors may be used in various combinations with each other or with insulin when treatment targets are not achieved. Combination therapy capitalises on the complimentary modes of action of the different drug classes, and there is some evidence to suggest that the use of combination therapy (at submaximal doses of each drug) is superior to monotherapy in terms of glycaemic control, with no increase in side effects.²⁵ Fixed-dose combination tablets are now available, and may be a convenient way of administering oral combinations.

Insulin

Insulin is most commonly used when adequate glycaemic control can no longer be achieved with oral agents alone. As type 2 diabetes is a progressive disorder, with loss of beta cell function occurring over time, insulin is often needed to achieve good glycaemic control, and should be considered for all patients on maximum oral therapy whose HbA_{1c} is > 6.5%. Whilst inadequate glycaemic control, despite maximum oral therapy, may often be addressed by improving compliance with lifestyle goals, early treatment with insulin should be strongly considered when unintentional weight loss occurs at any time during the course of diabetes, including at the time of diagnosis.

Insulin should usually be combined with oral agents, as they limit the weight gain, and reduce the hypoglycaemia associated with insulin therapy,^{26,27} and there is evidence to suggest that metformin is important for cardiovascular protection.

Insulin should be considered as first-line therapy in lean symptomatic patients if there is uncertainty about the diagnosis of diabetes type. Further details regarding insulin usage can be found on pages 27–28. In addition, pages 29–33 discuss special situations where temporary insulin therapy may be required.

All patients starting insulin therapy should be counselled about the risks and symptoms of hypoglycaemia.

Chronic viral hepatitis is common in the Asian-Pacific region, and frequently co-exists with diabetes. When liver function is abnormal, use of oral hypoglycaemic agents may be problematic, and insulin is often the therapy of choice.

Selection (Phenotyping) for Appropriate Oral Hypoglycaemic Therapy

Obesity and other determinants

Obesity, particularly central (visceral) obesity, is a major factor in insulin resistance and will be an important determinant for choice of appropriate oral hypoglycaemic therapy. The criteria for obesity and its levels of associated risk for diabetes and CVD will vary between ethnic groups. For example, acceleration of cardiovascular risks has been demonstrated to be similar between Chinese communities (Hong Kong and Singapore) with body mass index (BMI) values > 23 kg/m² and European patients with BMI > 25 kg/m². By contrast, in Pacific Island communities, the opposite may apply. Waist circumference more accurately measures central obesity, and may be more useful than BMI (see Table 8, page 44 for cut-points). Other factors that may influence choice of therapy include availability, adverse effects, allergy, age and other medical conditions, e.g. renal or liver disease.

The Overweight or Obese Person with Diabetes

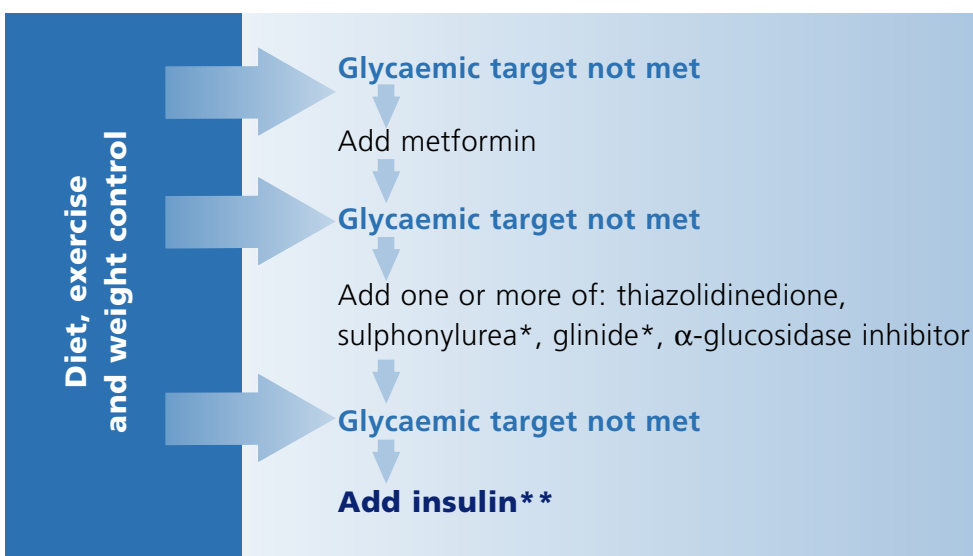


TABLE 4
*Management algorithm for **overweight** patients with type 2 diabetes mellitus.*

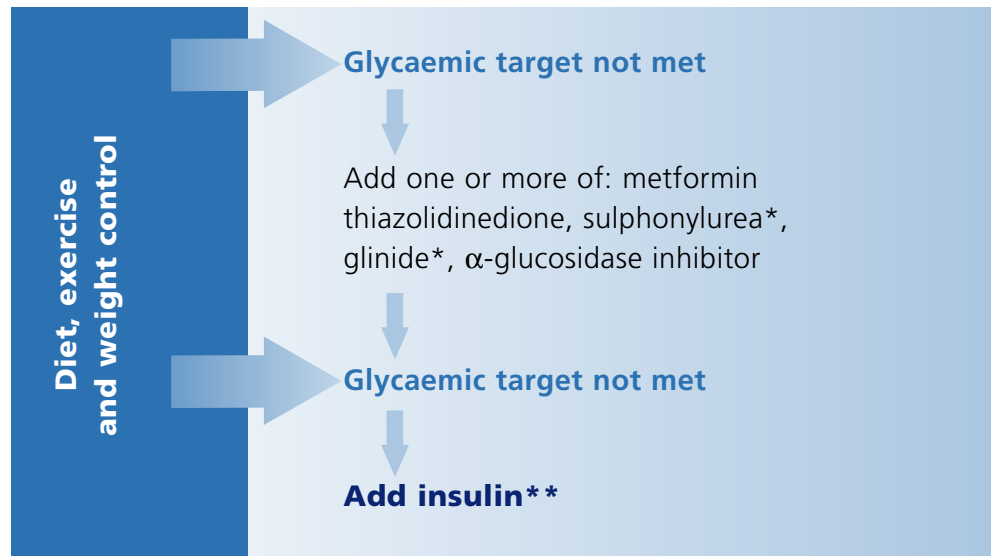
* Sulphonylureas and glinides should not be combined with each other.

** In some countries, combination of insulin with thiazolidinediones is not approved.

The Non-Obese Person with Diabetes

TABLE 5

Management algorithm for **normal weight** patients with type 2 diabetes mellitus.



* Sulphonylureas and glinides should not be combined with each other.

** In some countries, combination of insulin with thiazolidinediones is not approved.

Guidelines for commencing insulin

- Continue oral hypoglycaemic agents
- Intermediate-acting/long-acting insulin at bedtime
- Initial dose 0.2 units/kg
- Monitor FPG
- Aim for FPG 4–8 mmol/L (72–144 mg/dl) (individualise)
- Adjust insulin by 2–4 units every 3–4 days until FPG target is met[†]

[†] Proceed to twice-daily insulin if daytime blood sugars or HbA_{1c} are elevated, and nocturnal hypoglycaemia is occurring.

Special Situations

Children and adolescents

In principle, the pharmacological treatment of hyperglycaemia is similar in adults and children.⁸ However, there are many special problems in dietary and therapeutic management as a result of the complex psychosocial aspects of adolescence, which mandate the involvement of the family, particularly in lifestyle changes. Furthermore, there are only limited data on pharmacological therapies for type 2 diabetes in adolescents and pre-adolescents.

Apart from insulin, there is limited approval for the use of oral hypoglycaemic agents in children, with metformin and rosiglitazone recently receiving approval in the USA.

Lack of adherence to management guidelines is common, and special efforts and skills in dealing with the adolescent age group are needed, since they face the same complications as adults with type 2 diabetes. The prospect of serious microvascular diabetic complications when these patients are in their early 30s, as well as accelerated macrovascular diseases, is a very real threat.



Management during illness

Metabolic control may deteriorate rapidly during illness of any kind. As part of their educational programme, it is important to instruct patients on actions to be taken.

- Do not stop diabetes tablets or insulin.
- Maintain fluid intake – clear soups, water, weak tea, etc.
- If unable to take food, substitute with fruit juice, regular soft drinks or other fluids containing glucose.
- Check blood glucose at least four-times daily.
- Test for urine ketones at least twice daily.
- If vomiting, diarrhoea or drowsiness persist, a physician should be called immediately.

The DIGAMI study showed a clear reduction in mortality when intensive insulin therapy was used for people with an acute myocardial infarction and an elevated admission blood glucose.²⁸ However, the follow-up study failed to confirm this benefit; this may have been due to the frequent use of intensive insulin therapy in the control arm as well as in the intervention arm.²⁹

Pregnancy

Type 2 diabetes is increasingly common in women of childbearing age and can have a devastating impact on the growing baby.³⁰ All women with the potential to become pregnant need to have good pre-conceptual care to avoid significant risk of foetal malformations and early foetal loss. This includes:

- Pre-conceptual counselling, including complication screening, and where appropriate, contraception advice until targets have been achieved
- Optimising glycaemic control, preferably with a normal HbA_{1c}
- Folate supplementation (5 mg/day)
- Stopping statins and reviewing antihypertensive medications to avoid those contraindicated in pregnancy³¹
- Replacing oral hypoglycaemic agents with insulin therapy wherever possible.

Women with undiagnosed type 2 diabetes who become pregnant have a particularly high chance of damaged babies, and screening for gestational diabetes will detect such women, and reduce the risk of adverse perinatal outcomes.³²

During pregnancy, tight glycaemic control and close obstetric monitoring is required, with early intervention where necessary. For optimal diabetes management:

- All women should check their blood glucose at least four times daily, including after meals. Targets are: fasting/pre-prandial < 5.5 mmol/L (100 mg/dl); post-prandial < 7.0 mmol/L (126 mg/dl) at 2 hours.
- Insulin requirements need to be tailored to the individual, with most women using basal-bolus regimens, including 4–5 injections each day. Insulin requirements are lower in the first trimester and can drop in the third trimester, so close monitoring and adjustment of insulin therapy is necessary. While the short-acting insulin analogues are considered safe in pregnancy, there is insufficient evidence for long-acting insulin analogues, and these should be avoided.
- Oral hypoglycaemic agents are not recommended for use in pregnancy.
- Eyes should be tested for retinopathy and its progression in each trimester.

Surgery

- Special attention to management is required in the patient with type 2 diabetes undergoing surgery. This involves communication between the GP, diabetes specialist, anaesthetist and surgeon.



- Patients with type 2 diabetes should be assessed several weeks prior to surgery for general physical status, degree of diabetes control and suitability for anaesthesia. On the day of surgery, oral hypoglycaemic agents should usually be omitted.
- Intra-operative blood sugars of 5.0–11.0 mmol/L should be maintained. For major surgery, this will require an intravenous insulin infusion and frequent blood glucose monitoring. A combined glucose-insulin-potassium infusion is a simpler alternative to separate insulin and glucose infusions.³³
- For patients requiring post-operative intensive care with ventilation, a blood sugar of 4.5–6.0 mmol/L is the ideal, and has been shown to reduce mortality and morbidity.³⁴ A slightly more conservative target of 6.0–10.0 mmol/L, may be more appropriate in some settings.

Tight glycaemic control in the peri-operative period is the ideal, but requires an experienced team and frequent blood glucose monitoring.

The elderly

- Elderly patients may be on multiple drug therapies; therefore, the aim of treatment should be to avoid hypoglycaemia, with reasonable control of hyperglycaemia.
- The benefits of tight glycaemic control may take 10 years to appear, so less aggressive glycaemic targets are often appropriate for the elderly. Regular review of nutrition should be conducted by a dietician and exercise should be encouraged.
- When glycaemic targets are not met with diet alone, an α -glucosidase inhibitor or low doses of sulphonylureas are acceptable.
- Metformin is often contraindicated in elderly patients, because of co-existing renal, liver or cardiovascular impairment. Sulphonylureas should be used with caution because of the risk of hypoglycaemia.



Psychiatric disorders, HIV/AIDS and diabetes

The side effects of certain therapies for psychiatric disorders and HIV/AIDS may result in the precipitation or worsening of diabetes, and in elevated risk of CVD. Some antipsychotics (particularly the second-generation agents) increase the risk of obesity, type 2 diabetes and dyslipidaemia – integral components of the metabolic syndrome. The effect may vary with different drugs. The ADA has recently published a consensus statement on antipsychotic drugs and diabetes.³⁵ Dyslipidaemia and insulin resistance are also associated with highly active antiretroviral therapy used for HIV/AIDS, particularly with the protease inhibitor drugs.³⁶ It is advisable that therapy

for patients with mental illnesses and those with HIV be chosen very carefully, taking into consideration a number of factors, particularly the risk of diabetes and CVD.

Prior to initiating these therapies, patients should undergo screening with fasting blood glucose and lipids (other risk factors such as blood pressure, obesity, family history and smoking should also be reviewed).

Recommendations for antipsychotics include measurement of blood glucose and weight each month for the first 6 months of therapy. At the very least, weight should be monitored regularly, with blood tests reserved for those who gain weight.

Ultimately, to provide patients with optimum care, the medical practitioner should balance the potential therapeutic benefit of a treatment for these conditions with the possible associated metabolic complications.

Steroid therapy

Steroids are widely used to treat a variety of inflammatory disorders, and can have important effects on glucose metabolism, leading to the precipitation or worsening of diabetes. This is usually dose-dependent, and can occur in chronic administration, or as a result of a single dose (e.g. intra-articular injections). After the course of steroids has finished, glucose metabolism usually returns to its prior state. However, after prolonged courses, this is not always the case.

For those without diabetes, who are starting a course of steroids, screening for diabetes should be done before and at regular intervals during the course.

For those with diabetes, blood sugars should be checked closely throughout the period on steroids. The typical pattern of blood sugars for those on steroids usually includes relatively normal levels on fasting, but marked elevations as the day progresses. Therefore, monitoring of fasting blood sugars alone is inadequate. Increases in hypoglycaemic therapy are often required, are very variable in magnitude, and can often be implemented on the first day of steroid therapy. As steroid doses are changed, hypoglycaemic therapy should also be revised, and alterations to hypoglycaemic therapy can often be made on the same day as steroid dose changes are made.

Infections in the diabetic patient

Diabetes control may be seriously affected by intercurrent infections, many of which occur with greater frequency and severity in patients with pre-existing poor glycaemic control. Infection in diabetes precipitates a vicious cycle in which infection leads to uncontrolled hyperglycaemia, which in turn further aggravates infection.

The most common infections in people with diabetes are urinary tract infection (UTI), pneumonia, pulmonary tuberculosis (PTB), malignant external otitis and dental infections.

Urinary tract infection is common and more complicated in people with diabetes, and can lead to pyelonephritis and septicaemia,³⁷ with *Escherichia coli* and *Klebsiella* being the most common organisms. Fungal infections with candida species can cause cystitis, renal and perinephric abscesses. Vaginal pruritus is a very common manifestation of vaginal fungal infection.

Pneumonia remains an important infection amongst people with diabetes. The usual organisms are streptococci, staphylococci, and gram-negative rods. Fungal respiratory infections with aspergillosis and mucormycosis are also more common in people with diabetes.

Numerous studies have shown that people with diabetes are more prone to tuberculosis (TB) than are those without diabetes. In a population-based cohort of patients with pulmonary TB, 29.7% had previously diagnosed diabetes.³⁸ Atypical radiological images of pulmonary TB are common in people with diabetes, with one series showing that more than 70% had lower lung lesions and cavitation.³⁹ Multiple drug-resistant TB is also common in diabetes.

The skin is a common site of staphylococcal infection in patients with diabetes, usually occurring in the lower extremity area. Infected foot ulcers frequently involve several organisms, the most common of which are staphylococci, streptococci, gram-negative rods and anaerobes. Fournier's gangrene can occur with perineal infections, and can be fatal. Peridontitis is seen with increased frequency in people with diabetes and causes loosening of the teeth. Good dental hygiene is imperative. Malignant external otitis is often missed as a cause of infection in patients with diabetes.

Hypoglycaemia

Hypoglycaemia is a potentially serious complication of treatment in type 2 diabetes patients, especially among the elderly, people with renal insufficiency and people with severe micro- and macroangiopathy.

The risk of hypoglycaemia is increased with strict control as is the chance of weight gain; therefore, flexibility should be exercised in individual cases. Hypoglycaemia occurs with insulin, sulphonylureas and glinides, but not with other classes of hypoglycaemic agents.

Patients receiving certain sulphonylureas (chlorpropamide, glibenclamide) or insulin are particularly at risk. The risk is highest in the elderly, and in those patients with renal failure or liver disease, and is particularly difficult to detect and troublesome to manage when it occurs at night. Glargine insulin is associated with less hypoglycaemia than is NPH insulin.⁴⁰

Some herbal and traditional medicines can be associated with hypoglycaemia, as they may contain glucose-lowering agents or may affect renal or liver function.

Causes of hypoglycaemia and response

Insulin or sulphonylurea and glinides

At the beginning of treatment, the doctor should start with a low dose and gradually increase, adjusting the dose carefully.

Decrease, delay or omission of meals

Patients should have a stable amount of food, regular meal times and should decrease drug dosage if they cannot tolerate their usual amount of food.

Increase of physical exercise

Extra complex carbohydrates should be eaten before exercising.

Excessive alcohol intake, particularly without food

Alcohol can lead directly to hypoglycaemia. Binge drinking, and consuming alcohol without food, should be avoided.

Behavioural disturbances and other unusual symptoms are more frequent in elderly patients with hypoglycaemia. Hypoglycaemia does not occur during dietary, α -glucosidase inhibitor or metformin therapy. However, the combination usage with other agents may cause hypoglycaemia.



Action

If hypoglycaemia is suspected, a blood glucose level measurement is needed to confirm the diagnosis.

Note: If blood glucose levels cannot be measured, treat as hypoglycaemia.

The conscious patient

Administer an oral carbohydrate, such as sugar or glucose.

Note: Hypoglycaemia induced by the longer-acting sulphonylureas (or long-acting insulin) can be prolonged. It is important to monitor glucose levels for at least 24–48 hours after the patient regains consciousness.

A long-term glucose infusion may be needed and the patient should be admitted to hospital.

The unconscious patient

Administer 20 ml 50% glucose intravenously or 0.5–1 mg glucagon intramuscularly. Provide oral carbohydrates as soon as the patient is conscious.

Note: Hypoglycaemia induced by the longer-acting sulphonylureas (or long-acting insulin) can be prolonged. It is important to follow glucose levels for at least 24 hours. A long-term glucose infusion may be needed and the patient should be admitted to hospital.



The most important chronic complications of type 2 diabetes are those affecting blood vessels and nerves.

The microvascular complications (retinopathy, nephropathy and neuropathy) are relatively specific to diabetes and the risk of these (particularly retinopathy) is used to help define the diagnostic criteria for diabetes. The risk of these complications is related to duration of diabetes as well as degree of hyperglycaemia. However, due to delayed diagnosis, these complications may already be present at diagnosis; and coexisting hypertension or dyslipidaemia may exacerbate their risk.

Retinopathy and Blindness

The primary risk factors for diabetic retinopathy are duration of diabetes, poorer glycaemic control, elevated blood pressure and hyperlipidaemia. Other risk factors include pregnancy and the presence of diabetic nephropathy.

Patients with type 2 diabetes are also at higher risks of other eye diseases, including cataract, glaucoma, retinal vascular occlusions and ischaemic optic neuropathy.

Diabetic retinopathy is a leading cause of blindness among working-age adult populations.⁴¹ Approximately 20–40% of adults with type 2 diabetes have some signs of retinopathy, and about 8% have more severe vision-threatening retinopathy.⁴² Diabetic retinopathy is classified into an earlier stage called non-proliferative diabetic retinopathy (NPDR) and a later, more advanced stage called proliferative diabetic retinopathy (PDR). In NPDR, microaneurysms, haemorrhages, hard exudates, cotton wool spots, intraretinal microvascular abnormalities and venous beading are common ophthalmoscopic features. PDR is characterised by the presence of new abnormal blood vessels, vitreous haemorrhage and fibrous scarring. An additional complication of NPDR is the development of macular oedema, characterised by swelling and hard exudate deposition near the central macula.

Screening

- Comprehensive, dilated eye examinations and assessment of visual acuity by trained personnel every 1–2 years from the time of diagnosis.
- More frequent examinations are required if retinopathy is detected (e.g. every 6–12 months for mild NPDR and 3–6 months for more severe retinopathy).

Management

- Aggressive control of hyperglycaemia, hypertension^{21,23,43} and dyslipidaemia prevents development, and slows progression of retinopathy.
- Referral to an ophthalmologist if any of the following are present:
 - Proliferative or preproliferative retinopathy.
 - Macular oedema or retinal changes within 1 disc diameter of the fovea.
 - Inability to clearly visualise the retina (e.g. due to cataract).
 - Unexplained reduction in visual acuity.
- Timely laser photocoagulation for severe retinopathy is effective in preventing visual loss.^{44,45}

Nephropathy

Diabetic nephropathy is the most common cause of renal failure in many countries, and there is a particularly large burden of nephropathy in the Asia-Pacific region.⁴⁶ The earliest stages are evidenced by an increase in urinary albumin excretion (microalbuminuria), progressing to macroalbuminuria or overt proteinuria, with a subsequent rise in serum creatinine, eventually leading to renal failure and the need for dialysis and transplantation. In parallel to the progressive decline in renal function, there is a significant increase in the risk of cardiovascular disease, which is manifest even at the stage of microalbuminuria. Thus, it is vital to view microalbuminuria, and the more advanced stages of nephropathy, as risk factors for CVD, as well as for renal failure.

Screening

- Screening for nephropathy should be performed annually.
- The minimum requirement is to dipstick the urine for protein. This will detect overt proteinuria (and some other non-diabetic renal diseases), but will miss microalbuminuria.
- The simplest test for microalbuminuria is a urinary albumin:creatinine ratio, which can be performed on a spot urine sample. If the levels are abnormal, the test should be repeated within 3 months to confirm the diagnosis.
- Microalbuminuria – albumin:creatinine
 - Men: 2.5–25.0 mg/mmol (22–220 mg/g)
 - Women: 3.5–25.0 mg/mmol (31–220 mg/g)
- Macroalbuminuria – albumin: creatinine > 25.0 mg/mmol (220 mg/g) (men and women).
- Serum creatinine should be measured annually.

Management

- An ACE inhibitor or angiotensin II receptor blocker should be used, even if blood pressure is normal.^{47–49} Serum creatinine and potassium levels should be checked within 1–2 weeks of starting these agents.
- Blood pressure should be managed aggressively, aiming for a target of < 130/80 mmHg.
- Multiple antihypertensive drugs are often needed.
- Aggressive management of other cardiovascular risk factors, especially lipids, and of blood glucose is needed.
- The possibility of the presence of non-diabetic renal disease should be considered, especially in the presence of persistent haematuria or elevated serum creatinine in the presence of minimal proteinuria.

Diabetic Foot Problems

People with diabetes are, in general, up to 30 times more likely to require a lower limb amputation compared with the general population.⁵⁰ Hence, lower limb amputation is one of the most feared complications of diabetes.

Diabetic foot problems result from complex interactions between peripheral neuropathy (including autonomic dysfunction), peripheral arterial disease, and poor foot hygiene. The relative contributions of each may vary from patient to patient and may also vary in different populations; for example, the contribution from peripheral arterial disease may be less in some Asian populations.

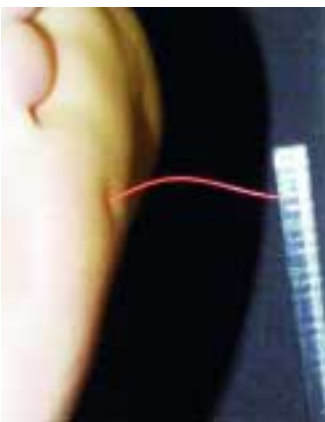
Diabetic neuropathy

There are many manifestations of diabetic neuropathy, but the most common, and most important is peripheral neuropathy. This insidious loss of distal sensation is frequently asymptomatic, but nevertheless leads to a high risk of foot ulceration and amputation. A minority of patients with peripheral neuropathy have associated pain. This usually occurs in the feet, is often burning and tingling in nature, and is typically worse at night than during the day. Treatment of the pain is often unsatisfactory, but the best evidence of efficacy is for tricyclic antidepressants, and the anticonvulsant,⁵¹ gabapentin.⁵² All patients with peripheral neuropathy should be given foot care advice, as it reduces the chances of foot ulceration.⁵³

Peripheral arterial disease

Peripheral arterial disease is common in people with diabetes. It may present with typical symptoms of intermittent claudication, but is often asymptomatic, and an ischaemic foot ulcer may be its first presentation. Exercise is beneficial in the early stages.⁵⁴ Surgery or angioplasty should be considered for progressive symptoms of claudication, and for ischaemic ulceration.

FIGURE 3



Foot screening

- Perform annually in all patients with diabetes.
- Risk of neuropathic foot ulceration is most easily detected using a 5.07/10 g Semmes Weinstein monofilament (Figure 3). Insensitivity at any site on the foot indicates risk of neuropathic ulceration.
- Lesser degrees of neuropathy can easily be detected by standard clinical assessments.
- Palpation of foot pulses (dorsalis pedis and posterior tibial) is the simplest means of identifying peripheral arterial disease.
- Check for skin cracks, infection, state of the nails, callus (a sign of repetitive pressure), deformities and suitability of footwear.

Foot care education

Detailed foot care education should be provided to all people with previous ulceration or evidence of peripheral neuropathy or peripheral arterial disease. The key elements of foot care education are:

- No barefoot walking, including on sand and in the water.
- Inspect feet every day, and report any skin breaks or areas of redness or swelling to a healthcare professional.
- Check footwear for foreign objects before putting on.
- Keep feet clean, and apply moisturising cream to dry skin.

Reinforce foot care education regularly.

Foot ulceration

Diabetic foot ulcers are typically due to neuropathy, peripheral arterial disease or poor foot hygiene, and are frequently precipitated by inappropriate footwear.

Neuropathic ulcers are usually seen at sites of repetitive pressure, such as the plantar surface of the metatarsal heads, and on the dorsum of the toes (Figure 4). They are usually painless, surrounded (or covered) by callus, and clinical examination reveals sensory loss.

Ischaemic ulcers typically occur at the tips of the toes and on the heel (Figure 5). They are often painful, and foot pulses are usually absent.

Principles of treatment of diabetic foot ulcers

1. Pressure relief – where repetitive pressure has caused the ulcer, this must be relieved. This is vital for neuropathic ulcers, and may involve removal of callus and wearing of appropriate shoes or a pressure-relieving cast.
2. Improvement of vascular supply (by surgery or angioplasty) – this is often needed for ischaemic ulcers.
3. Regular debridement of infected and necrotic tissue.
4. Aggressive treatment of infection, where clinical signs of infection are present (growth from swabs in the absence of clinical signs usually indicates colonisation not infection).

FIGURE 4



FIGURE 5



Macrovascular Comorbidities, Dyslipidaemia and Hypertension

The macrovascular complications (coronary heart disease, cerebrovascular disease and peripheral vascular disease) are not specific to diabetes:

- Diabetes increases the risk of the development of CVD 2–4 times.⁵⁵ It also predisposes patients to more severe and generalised disease, with a worse prognosis, and to onset of problems at a younger age.
- Among Asian populations, stroke is the most common form of CVD,⁵⁶ and the relationship between BP and stroke is stronger among Asians than Europeans.⁵⁷
- An increased risk of CVD is already apparent with elevation of fasting and 2-hour glucose that remain below those reaching levels diagnostic of diabetes.^{58,59}

Hypertension

Patients with persistent BP values > 130/80 mmHg should be treated, with the aim of achieving BP < 130/80 mmHg,^{60,43} and reducing the risk of both CVD and microvascular complications.

Initial treatment involves lifestyle interventions focused on exercise, weight loss and restriction of salt and alcohol intake.

If lifestyle modification does not achieve the target BP, pharmacological treatment with a drug from any of the following classes should be initiated:

- ACE inhibitors^{47,61,62}
- angiotensin II receptor blockers⁶³
- beta-blockers⁶¹
- calcium channel blockers⁶⁴
- thiazide-like diuretics.⁶²

ACE inhibitors or angiotensin II receptor blockers should be used as first-line in the presence of nephropathy.

Combination therapy is frequently required to achieve target BP.

Blood pressure should be measured at every clinic visit.



Dyslipidaemia

Elevated triglycerides and low HDL occur much more commonly in people with type 2 diabetes than in the general population. Elevated total- and LDL-cholesterol are no more common in the diabetic population, but are nevertheless very frequent in the whole population. Strong evidence exists for the benefit of statins in reducing cardiovascular risk,⁶⁵ while the evidence for the benefit of fibrates is less strong.⁶⁶

- Statins should be used in all those with previous CVD, irrespective of current lipid levels,⁶⁵ with the aim of achieving LDL < 2.5 mmol/L.
- For those without CVD and > 40 years of age, statins should be used if LDL \geq 2.5 mmol/L or if total cholesterol \geq 4.5 mmol/L. For those < 40 years, statins should be considered if other cardiovascular risk factors (hypertension, smoking, microalbuminuria, family history of premature CVD or elevated calculated total cardiovascular risk) are also present.
- Once LDL targets are achieved, fibrates should be considered if triglycerides are \geq 1.5 mmol/L or HDL \leq 1.1 mmol/L.
- Triglyceride lowering should be used if triglycerides are \geq 4.5 mmol/L to prevent pancreatitis.
- Consideration should be given to the use of other lipid-lowering drugs (e.g. ezetimibe, sustained release nicotinic acid, concentrated omega 3 fatty acids) in those who fail to reach lipid targets or who are intolerant of conventional drugs.
- All patients with abnormal lipid levels should have intensified lifestyle interventions.

Aspirin therapy

Antiplatelet therapy with aspirin reduces the risk of CVD, but increases the risk of gastrointestinal and cerebral haemorrhage. The evidence for overall benefit of aspirin in people with diabetes and known CVD is very strong, but less so in those without CVD.⁶⁷

- Low-dose aspirin should be used in all those with previous CVD, unless specific contraindications exist.
- Low-dose aspirin should be considered in all those without previous CVD, but with additional cardiovascular risk factors.

Lipids should be measured at least once per year.



Chronic Complications

ACE inhibitors

The HOPE study clearly showed that the addition of ramipril to other therapy reduced mortality in people with diabetes who were aged > 55 years of age and had one or more additional CVD risk factor.⁴⁷ Thus, ACE inhibitors are recommended in this group, irrespective of BP.

TABLE 6
Routine screening requirements.

	Minimum screening frequency	Screening procedure
Eyes	2 years	<ul style="list-style-type: none"> • Fundus exam through dilated pupils • Visual acuity
Kidneys	1 year	<ul style="list-style-type: none"> • Urinary albumin measurement
Feet	1 year	<ul style="list-style-type: none"> • Clinical neurological and vascular assessment • Inspection of feet and footwear
Blood pressure	Each visit	<ul style="list-style-type: none"> • Measure seated after 5 minutes rest
Lipids	1 year	<ul style="list-style-type: none"> • Blood lipids
Glycaemic control	6 months	<ul style="list-style-type: none"> • HbA_{1c}

Cessation of cigarette smoking and reduction of alcohol consumption should be addressed.

In order to minimise the risk of macrovascular disease, it is essential to pay strict attention to all treatable risk factors. It is a mistake to focus on treating the hyperglycaemia alone.

It is important to be constantly on the alert for macrovascular disease. In addition, it should be remembered that, as a result of coexisting autonomic neuropathy, angina and myocardial infarction may be 'silent' due to the absence of pain. Unfortunately, ischaemic heart disease cannot easily be detected by physical examination.

Resting ECGs have limited value; thus, in patients thought to be particularly vulnerable (e.g. those with additional risk factors such as a strong family history, smoking, hypertension and dyslipidaemia) stress testing is necessary to evaluate cardiac disease.

Thrombolytic therapy in acute myocardial infarction is safe in diabetes, even in the presence of retinopathy. Beta-blockers post-infarction appear to be equally effective in people with diabetes compared with the general population.

The Metabolic Syndrome

The clustering of hyperglycaemia, obesity, dyslipidaemia and hypertension has been labelled the metabolic syndrome, dysmetabolic syndrome or insulin resistance syndrome. The clustering of these parameters indicates common underlying aetiological factors, and the clinical importance of the metabolic syndrome is the high cardiovascular risk associated with it.

A number of expert groups have proposed different definitions for the metabolic syndrome. The most accepted of these definitions have been produced by the WHO, The European Group for the study of Insulin Resistance, and the National Cholesterol Education Program Adult Treatment Panel III. More recently, the IDF has proposed a new definition, which makes central obesity a necessary requirement, and, for the first time, provides different obesity cut-points for different ethnic groups.

Central obesity	Waist circumference* – ethnicity specific
+	any two of the following
Raised triglycerides	≥ 1.7mmol/L (150 mg/dl) <i>or</i> specific treatment for this lipid abnormality
Reduced HDL-cholesterol	< 1.03 mmol/L (40 mg/dl) in males < 1.29 mmol/L (50 mg/dl) in females <i>or</i> specific treatment for this lipid abnormality
Raised blood pressure	Systolic : ≥ 130 mmHg <i>or</i> Diastolic: ≥ 85 mmHg <i>or</i> treatment of previously diagnosed hypertension
Raised plasma glucose**	Fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dl) <i>or</i> previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dl, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

TABLE 7

The IDF consensus worldwide definition of the metabolic syndrome.

* If BMI is > 30 kg/m², then central obesity can be assumed, and waist circumference does not need to be measured.

** In clinical practice, IGT is also acceptable, but all epidemiological reports of the prevalence of the metabolic syndrome should use only the fasting plasma glucose and presence of previously diagnosed diabetes to assess this criterion. Prevalences also incorporating the 2-hour glucose results can be added as supplementary findings.

The Metabolic Syndrome

TABLE 8
Country-/ethnic-specific values for waist circumference.

Country/ethnic group	Waist circumference (as measure of central obesity)	
Europeids		≥ 94 cm
		≥ 80 cm
South Asians		≥ 90 cm
		≥ 80 cm
Chinese		≥ 90 cm
		≥ 80 cm
Japanese		≥ 85 cm
		≥ 90 cm

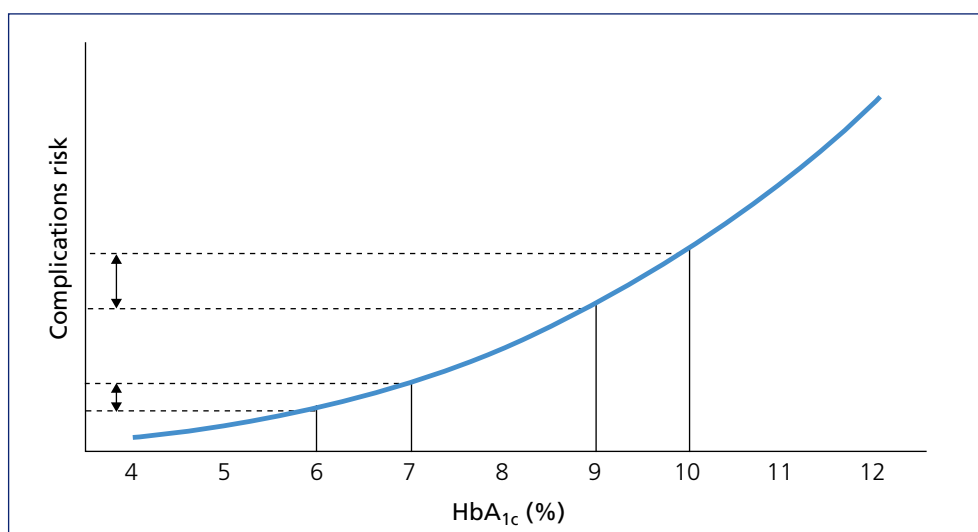
These are pragmatic cut-points and better data are required to link them to risk. Ethnicity should be the basis for classification, not country of residence.

Recognition of these features in people with type 2 diabetes has special importance, as it indicates the need for aggressive CVD risk reduction. Fortunately, there are treatment regimens that can influence all of these risk factors. Weight reduction and exercise reduce both insulin resistance and hyperinsulinaemia, as well as improving glucose tolerance and other CVD risk factors. Smoking should be prohibited and alcohol consumption should be moderated.

Targets for Control

Table 9 summarises the key treatment targets identified in the earlier chapters. Each value is both a threshold for intervention and a target for treatment. These are ideal targets, and it should be remembered that personal, social or environmental factors may make it unreasonable to aim for these targets. In particular, strict targets may be inappropriate for the elderly, as the benefits of overly aggressive drug treatment (especially of hyperglycaemia) may be outweighed by the side effects and costs.

Many of these targets are based on results from studies conducted in Europe and North America; it is important for individual countries to use these as a basis for the formulation of guidelines targeted at their own populations.



All improvements are beneficial, whether or not a target is reached.

Failure to reach a target should not be seen as failure to achieve a benefit, as all improvements in risk factors will reduce risk. Indeed, lowering HbA_{1c} from 10% to 9% will have a greater impact on reducing risk of complications than will lowering the HbA_{1c} from 7% to 6% (Figure 6).

FIGURE 6

Improvement in risk associated with a 1% reduction in HbA_{1c}, from 10% to 9%, and from 7% to 6%.

Parameter	Target
HbA_{1c}	6.5%*
BP	130/80 mmHg
Total cholesterol	4.5 mmol/L (174 mg/dl)
LDL-cholesterol	2.5 mmol/L (97 mg/dl)
HDL-cholesterol	1.0 mmol/L (39 mg/dl)
Triglycerides	1.5 mmol/L (133 mg/dl)
Urinary albumin:creatinine	2.5 mg/mmol (22 mg/g) – men 3.5 mg/mmol (31 mg/g) – women
Exercise	150 min/week

*Value applies to a DCCT-aligned assay.

TABLE 9

Targets for control and thresholds for intervention.

Lifestyle and Pharmacological Approaches

The rapid escalation of the number of people with type 2 diabetes in the Asian-Pacific region calls for urgent action on prevention. If not, the economic costs of premature morbidity and mortality from diabetes could shatter the healthcare budgets of both developing and affluent nations. By 2010, Asia will be home to 61% of the total global projected number of people with diabetes.

Recent studies have shown the potential for intervention in IGT patients to reduce progression to type 2 diabetes. One such study is the Diabetes Prevention Program in the USA.²² This study showed that, over 3 years, lifestyle intervention (targeting diet and exercise) reduced the risk of progressing from IGT to diabetes by 58%, while the oral hypoglycaemic drug, metformin, reduced risk by 31%. Other large-scale studies from China,⁶⁸ Japan⁶⁹ and Finland⁷⁰ have also demonstrated the efficacy of lifestyle interventions. In the Finnish study, the cumulative incidence of diabetes after 4 years was 11% in the intervention group and 23% in the control group. During the trial, the risk of diabetes was reduced by 58% in the intervention group. The reduction in the incidence of diabetes was directly associated with changes in lifestyle.

Several studies provide evidence that the lifestyle approach aimed at high-risk individuals, such as those with IGT, may not be sufficient to prevent all cases of type 2 diabetes. Pancreatic beta-cell function is often already substantially reduced at the time of clinical diagnosis of type 2 diabetes. Even at the earlier stage of IGT, beta-cell function is already impaired and intervention at this stage may be too late to prevent many cases of type 2 diabetes. Also, intensive intervention programmes using well-developed behaviour-modification approaches may show high relapse rates with weight gain and an increase in blood glucose after 1–2 years despite an initially encouraging response. Pharmacological therapy may, therefore, have a role. Currently, there is evidence that metformin,²² acarbose,²⁴



Prevention of Type 2 Diabetes

troglitazone,⁷¹ and the weight loss drug, orlistat,⁷² can reduce the incidence of type 2 diabetes in those at high risk.

We do not know yet whether treatment of IGT can delay or prevent the appearance of macrovascular disease, the major cause of morbidity and mortality in type 2 diabetes.

However, delaying the onset of diabetes in such high-risk patients will provide some benefit. It may, therefore, be prudent to treat people with IGT with lifestyle advice, at least, or with glucose-lowering agents of proven long-term safety while more data are accumulated. However, until studies are completed investigating the impact of these, and other, agents on hard clinical end-points in people with IGT, their role in IGT will remain uncertain.

National governments have been slow to react to the emerging problem of the diabetes epidemic. Urgent action is needed to address prevention issues, as has been taken for emerging communicable diseases such as AIDS. The diabetes epidemic will not be prevented by clinical interventions targeting diet and exercise alone in people presenting to medical services. Major and dramatic changes will be needed at a societal level to increase the amount of physical activity undertaken, and to improve the availability and desirability of healthy food. The benefits of improvements in lifestyle for the whole community are likely to be seen, not only in the prevention of diabetes, but also reductions in rates of other diseases – such as CVD and certain cancers – socioeconomic and cultural status.



Initial Visits

Set individual targets for treatment

Body weight kg	} BMI (kg/m ²)
Height cm		
Waist circumference cm		
Blood glucose			
fasting/post-prandial mmol/L	(..... mg/dl)
Blood pressure (syst/diast) mmHg		
Total cholesterol mmol/L	(..... mg/dl)
HDL-cholesterol mmol/L	(..... mg/dl)
Triglycerides mmol/L	(..... mg/dl)
HbA _{1c} %		
Albuminuria* mg/g		

Specify and plan first aims and actions with patient

For example:

- Physical activity.
- Nutritional advice.
- Stop smoking.
- Reduce body weight by kg in weeks.
- Perform self-monitoring.
- Start record book.

Later visits

- Discuss results, including HbA_{1c}, and specify next aims and actions with patient.
- Check diabetes record book, discuss results, nutrition and exercise.
- If hypertensive, consider specific treatment; start early if nephropathy (including albuminuria*) is present.
- If dyslipidaemia is present, stress nutritional modifications and consider specific drug treatment.
- Reduce body weight further by kg in weeks.

*Microalbuminuria if resources are available

Clinical Monitoring Protocol

Test	Initial visit	Follow-up visit	Quarterly visit	Annual visit
Eye: visual acuity funduscopy				
Feet: pulses neuropathy				
Weight				
BMI				
Blood pressure				
Blood glucose				
HbA _{1c}				
Cholesterol/HDL-cholesterol				
Triglycerides				
Albuminuria*				
Creatinine/BUN				
ECG				
Urine microscopy				

- = Conduct test
- = No test required
- = Conduct test if abnormal first visit

*Microalbuminuria if resources are available

Appendix I

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Appendix II

The following reports and guidelines on type 2 diabetes are also available:

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- (v) World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications*. Report of a WHO Consultation. WHO/NCD/NCS/99.2. Geneva: WHO, 1999.

Appendix III

*Aetiological classification of disorders of glycaemia**

Type 1	Beta-cell destruction, usually leading to absolute insulin deficiency Autoimmune Idiopathic
Type 2	May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance
Other specific types	Genetic defects of beta-cell function Genetic defects in insulin action Diseases of the exocrine pancreas Endocrinopathies Drug- or chemical-induced Infections Uncommon forms of immune-mediated diabetes Other genetic syndromes sometimes associated with diabetes
Gestational diabetes**	

* As additional subtypes are discovered, it is anticipated that they will be reclassified within their own specific category.

** Includes the former categories of gestational IGT and gestational diabetes.

Source – WHO Consultation Report: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications*, 1999.

Appendix IV

Disorders of glycaemia: aetiological types and clinical stages

Stages	Normoglycaemia	Hyperglycaemia	Diabetes mellitus		
	Normal glucose tolerance	IGT and/or IFG	Not insulin requiring	Insulin requiring for control	Insulin requiring for survival
Type 1 Autoimmune Idiopathic					
Type 2* Predominantly insulin resistance Predominantly insulin secretory defects					
Other specific types*					
Gestational diabetes*					

* In rare instances, patients in these categories (e.g. Vacor toxicity, type 1 present in pregnancy) may require insulin for survival.

Source – WHO Consultation Report: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications*, 1999.

Appendix V

Conversion factors between conventional and SI units

This list is included to assist the reader to convert values between conventional units and the newer SI units (Système Internationale d'Unités) that have been mandated by many journals.

Analyte	SI units	Conventional units	SI to conventional units	Conventional to SI units
Plasma glucose	mmol/L	mg/dl	18.02	0.0555
Total cholesterol	mmol/L	mg/dl	38.61	0.0259
HDL cholesterol	mmol/L	mg/dl	38.61	0.0259
Triglycerides	mmol/L	mg/dl	88.5	0.0113

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Fourth edition

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