Diabetes mellitus is one of the most common noncommunicable diseases worldwide. In the Eastern Mediterranean Region there has been a rapid increase in the incidence of diabetes mellitus and it is now the fourth leading cause of death. The increasing prevalence of diabetes mellitus, the emergence of diabetes complications as a cause of early morbidity and mortality, and the enormous and mounting burden on health care systems make diabetes a priority health concern. These guidelines provide up-to-date, reliable and balanced information for the prevention and care of diabetes mellitus in the Region. The information is evidence-based and clearly stated to facilitate the use of the guidelines in daily practice. They are intended to benefit physicians at primary, secondary and tertiary level, general practitioners, internists and family medicine specialists, clinical dieticians and nurses as well as policy-makers at ministries of health. They provide the information necessary for decision-making by health care providers and patients themselves about disease management in the most commonly encountered situations.

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Guidelines for the prevention, management and care of diabetes mellitus

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Regional Office for the Eastern Mediterranean

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Guidelines for the prevention, management and care of diabetes mellitus

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Foreword

In the Name of God, the Compassionate, the Merciful

Diabetes mellitus is one of the most common noncommunicable diseases, and its epidemic proportion has placed it at the forefront of public health challenges currently facing the world. The World Health Organization (WHO) estimated the global burden of diabetes at 135 million cases in 1995, in a worldwide adult population of under 4 billion, and has projected that there will be 299 million cases by the year 2025. Although WHO recently accorded priority status to diabetes mellitus, many public health planners remain largely unaware of its magnitude and the seriousness of its complications. Of equal consequence, is the increasing prevalence of the disease and the long-term cost of therapy for both patients and the health sector, and its cost to nations in economic terms.

In the Eastern Mediterranean Region, there has been a rapid increase in the incidence of diabetes mellitus, consisting mainly of type 2. It is now the fourth leading cause of death in the Region. An estimated 22 million people have diabetes, out of a total adult population of 290 million. Studies conducted in different populations of the Region have reported high prevalence rates varying from 7% to 25% in the adult population. In addition, many countries are now reporting the onset of type 2 diabetes mellitus at an increasingly young age. People are presenting with type 2 in their twenties and thirties, and in some countries it is emerging in children. This pattern of younger age of onset extends the potential burden of therapy and complications to an even younger age group and for a longer period of an individual's lifespan.

There are a number of factors that might explain the increasing prevalence of diabetes mellitus in the Eastern Mediterranean Region, not least of all the significant social and economic changes which are being experienced. Rates of obesity are increasing, while people are becoming less physically active; both of these factors increase the risk of developing diabetes. In addition, the prevalence of diabetes mellitus increases with age, and there is evidence that the current life expectancy in the majority of Eastern Mediterranean countries now exceeds 65 years.

The WHO Regional Office for the Eastern Mediterranean has set goals and targets for diabetes mellitus prevention at the regional level. Because of the importance of diabetes and its complications in the Region, care should be considered a health priority and should be supported and strengthened by data collection, the establishment of national epidemiological studies, and the formulation of national plans. One promising initiative during the past few years has been the development of national diabetes control programmes in several countries of the Region; in others, committees to develop such

programmes have been set up, or diabetes has been integrated into noncommunicable disease programmes. The aim of integrating diabetes mellitus into primary health care is to establish routine screening procedures for the detection, monitoring and control of the common complications of diabetes. Treatment should not only target lowering of blood glucose level, but should also focus on the correction of other noncommunicable disease risk factors, such as smoking, dyslipidaemia, obesity, physical inactivity and hypertension.

As part of the efforts to improve health care, it is hoped that these regional guidelines will be useful in helping to standardize diabetes management at the primary, secondary and tertiary levels and in guiding policy-makers, particularly at ministries of health. Above all, we all need to work towards better prevention of diabetes mellitus in order to stop this rising burden in the Eastern Mediterranean Region.

Hussein A. Gezairy, MD, FRCS
Regional Director for the Eastern Mediterranean

Preface

The increasing prevalence of diabetes mellitus, the emergence of diabetes complications as a cause of early morbidity and mortality, and the enormous and mounting burden on health care systems make diabetes a priority health concern. This publication aims to provide up-to-date, reliable and balanced information for the prevention and care of diabetes mellitus in the Eastern Mediterranean Region. The prevalence of diabetes in the Region and the high morbidity that is associated with it stimulated the WHO Regional Office for the Eastern Mediterranean to develop these guidelines in order to address all practical issues relevant to the day-to-day management of glucose and its metabolic disorders, with respect to reduction in related morbidity and mortality.

The framework for the guidelines was discussed in the Regional Consultation on Diabetes Prevention and Care, Teheran, Islamic Republic of Iran, 2–5 February 2003. A consensus on major topics concerning diabetes prevention and care was formulated during the consultation and the conclusions reached are given in Annex 1. Because of the need for a standardized response to the challenge, the following regional strategies have been established for the prevention and care of diabetes: promotion of a healthy lifestyle; raising community awareness (eat less – walk more); primary prevention of diabetes; screening for type 2 diabetes mellitus; establishment of a regional training course for diabetes educators; and development of national strategy.

Management of diabetes mellitus, standards of care and clinical practical guidelines and *Health education for people with diabetes,* published by the Regional Office for the Eastern Mediterranean in 1994 and 1996, respectively, provided reliable guidance on management and education for diabetes in the Region. However, during the past 10 years, new developments and rapid changes in management and prevention have occurred. The present guidelines are intended to standardize management in the Region and include the latest, evidence-based information for diabetes. They provide the information necessary for decision-making by health care providers and patients themselves about disease management in the most commonly encountered situations. The information is evidence-based and clearly stated to facilitate the use of the guidelines in daily practice. The target population includes physicians at primary, secondary and tertiary level, general practitioners, internists and family medicine specialists, clinical dieticians, nurses and policy-makers at ministries of health. Accompanying this publication are three quick reference cards relating to the management of diabetes, management of diabetes and hypertension and management of diabetes and dyslipidaemia. These will provide primary health care workers, physicians, consultants and clinicians with a readily accessible appraisal of the evidence-based facts relating to diabetes.

Acknowledgements

The WHO Regional Office for the Eastern Mediterranean acknowledges with thanks the contributions of the participants at the Regional Consultation on Diabetes Prevention and Control (Annex 1) held in Teheran, Islamic Republic of Iran, 2–5 February 2003 whose discussions provided valuable input to this publication. WHO would also like to thank Fereiddoun Azizi, Imad M. El-Kebbi, Mohamad Reda Awadin and Ibrahim Sherif for their valuable input in reviewing the draft publication.

Chapter 1

Diabetes in the Eastern Mediterranean Region

Regional epidemiological status

In estimating the total number of persons with diabetes mellitus, we cannot rely solely on reported numbers of diagnosed cases. It is estimated that about one half of persons with diabetes are unaware of their disease and, even in industrialized countries, many individuals go undiagnosed. Although more recent data show that the proportion of undiagnosed cases has decreased, it is still at least about one quarter to one third of all persons with diabetes mellitus.

It is predicted that between 2000 and 2025, the size of the world's adult population will increase from less than 4 billion to 5.5 billion, mainly on account of a 60% increase in developing countries [1]. The number of adults with diabetes in the world is predicted to increase from 150 million in 2000 to 300 million in 2025 [2]. In industrialized countries, the number of diabetics will increase by about one third between 2000 and 2025, while in developing countries that number will more than double [2]. In 2025, more than 75% of the world's diabetic population will be living in developing countries.

Diabetes prevalence in some Eastern Mediterranean countries is among the highest in the world [3–16]. The Eastern Mediterranean Region extends from Pakistan in the east to Morocco in the west, and the population is a mosaic of several ethnic groups. The age distribution pattern of the population is pyramidal, with about 50% of the population aged below 20 years.

While the majority of persons with diabetes mellitus in industrialized countries are in the older age group, the majority in developing countries tend to be middle-aged and at the most productive stage of life [3]. Many Eastern Mediterranean countries are now reporting the onset of type 2 diabetes mellitus at an increasingly young age. Subjects are presenting in their second and third decade, and in some countries type 2 diabetes mellitus is emerging in children. This pattern of onset at a younger age extends the potential burden of therapy and complications to an even younger age group and for a longer period of an individual's lifespan [2,4–15]. In the Eastern Mediterranean Region as a whole, approximately half of the countries have published incidence rates. The highest rates are reported in Egypt, Kuwait, Lebanon, Oman and Qatar where the incidence of type 1 diabetes is reported to be 8–10 per 100 000 population per year in children aged <15 years while in Pakistan it is only 1 per 100 000 [4–14].

Over the past three decades, key social and economic changes have occurred in the majority Eastern Mediterranean nations. These include progressive urbanization, decreasing infant mortality and increased life expectancy. Increasingly sedentary lifestyles, the obesity pandemic and higher life expectancy have led to a dramatic rise in type 2 diabetes in many countries of the Region [4–14,16]. Traditional activities and dietary patterns that have sustained people over generations are rapidly disappearing and the socioeconomic situation in many countries has forced people to move to urbanized areas to seek employment, where they are less likely to lead a healthy lifestyle. Thus, it is estimated that in the Eastern Mediterranean Region 22 million people (out of a total adult population of 290 million) have diabetes mellitus, and it is predicted that this figure might increase to 30 million by 2025 [2,3]. In the Region, the diabetes prevalence rate for adults is 14.5%; however, recent studies conducted in different population groups have reported diabetes prevalence rates as high as 20% in the United Arab Emirates [12], 16% in Qatar and 15% in Bahrain. Even in much less affluent Pakistan the prevalence is 11% [4–14]. Studies in four countries of the Region (Bahrain, Kuwait, Oman and the United Arab Emirates) showed their current diabetes prevalence rates to be among the ten highest in the world, and a similar situation applies for impaired glucose tolerance (IGT) prevalence. As in many other countries with high diabetes mellitus prevalence, the onset of type 2 tends to occur at a relatively young age [5,7,10,12]. Table 1 shows the prevalence and estimated future prevalence of diabetes and IGT in the Eastern Mediterranean Region. Table 2 also shows the regional overview of diabetes in the Region.

Table 1. Prevalence and estimated future prevalence of diabetes and IGT in the Eastern Mediterranean Region [2]

All diabetes and IGT	2003	2025
Total population (millions)	544.6	839.2
Adult population, aged 20–79 years (millions)	276.0	493.6
Diabetes prevalence (%)	3.5–25	9–30
Diabetes numbers, aged 20–79 years (millions) (diagnosed and estimated undiagnosed	19.2–50	39.4–100
IGT prevalence, aged 20–79 years (%)	6.8–11	7.4–12
IGT number, aged 20–79 years (millions)	18.7–25	36.5–50

Table 2. Regional prevalence of diabetes (%)

Country	Male	Female
Afghanistan	–	–
Bahrain	24.4	35.9
Djibouti	–	–
Egypt	7.5	6.7
Iran, Islamic Republic of	9.8	11.1
Iraq	6.1	6.1
Jordan	14.9	12.5
Kuwait	14.7	14.8
Lebanon	14.9	9.7
Libyan Arab Jamahiriya	16.2	12.8
Morocco	8.6	8.2
Oman	11.8	11.3
Pakistan	11.1	10.6
Qatar	16	16
Saudi Arabia	26.2	21.5
Somalia	–	–
Sudan	3.5	3.4
Syrian Arab Republic	7.2	–
Tunisia	15.7	14.9
United Arab Emirates	21.5	19.2
Yemen	7.4	2

Regional status of diabetes care

While much work has been done in many countries to address diabetes, it is recognized that more is required. This is particularly true in the areas of screening prevention and early intervention. Diabetes is a costly disease in terms of morbidity, mortality and quality of life. It constitutes a considerable financial burden on individuals, their families, the health sector and governments.

In most countries of the Region, specialized diabetes centres are few and far apart and often not within reach of many people with diabetes [2-20]. Likewise, trained and experienced diabetologists are few, nutritionists and diabetes nurse educators are uncommon and chiropodists may be non-existent. Besides, the infrastructure at the primary care level is not capable of allowing meticulous implementation of the routine screening procedures, monitoring control and detecting common diabetes complications. In addition, provision of care for diabetes may differ in the same country, varying from very poor or almost non-existent care in some areas to highly structured care in other places [2].

In 2001, WHO carried out a global survey [17], the main objectives of which were to assess the current situation in relation to existing capacity for noncommunicable diseases, to identify constraints and needs and to set priorities for technical support to Member States. The majority of Eastern Mediterranean countries were found to have national plans for the prevention of diabetes and had already established national guidelines for the prevention and management (Table 3). More than 50% of Eastern Mediterranean countries reported having diabetes control plans. Effective preventive strategies, therefore, already exist but are not being rationally or widely utilized. The management of diabetes needs to be monitored through implementation of national strategies for optimal control of diabetes, hypertension, dyslipidaemia and obesity.

In the WHO Eastern Mediterranean Region, specifically, diabetes mellitus is an important public health disorder for many reasons. Not only are the risk factors associated with diabetes mellitus ever increasing, but the individual with diabetes frequently makes his or her decisions concerning the disease outside the clinical setting, either at home, on the job, or within his/her existing community. Many individuals are influenced by traditional beliefs, myths and misconceptions regarding the causes, symptoms and care of diabetes mellitus and continue to seek alternative measures for curing their condition. However, the disease is not only a problem for the individual but is also a societal challenge because of its serious complications and cost of treatment. Meanwhile, public awareness and understanding of diabetes remains very low in certain areas.

There are many important issues that the Region needs to address, not least of which is the lack of available mortality data. There is also a need for training of health professionals and paramedics on diabetes mellitus prevention and control. There is a lack of information on health care services management for diabetes mellitus as well as a lack of effort to assess the cost-effectiveness of the various interventions [18–20].

Table 3. Percentage of countries with national guidelines for prevention and management of major noncommunicable diseases

WHO region	Diabetes		Hypertension		Bronchial asthma		Common cancers	
	P	M	P	M	P	M	P	M
Africa	44	53	35	53	28	41	29	43
Americas	70	50	65	45	52	40	83	48
Eastern Mediterranean	89	50	70	64	33	22	60	33
Europe	82	64	82	53	69	45	84	59
South East Asia	67	67	50	67	17	33	43	43
Western Pacific	58	76	53	76	35	63	65	47
Total	69	61	63	59	47	44	67	48

P: prevention guidelines M: management guidelines

Chapter 2

Definition and classification

Definition

In 1999, WHO defined diabetes mellitus as "a metabolic disorder of multiple etiology, characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs" [21]. Thus, the metabolic abnormalities of diabetes result from inadequate insulin action on target tissues, due to deficient insulin secretion or insensitivity to insulin action, or a combination of both [2,22].

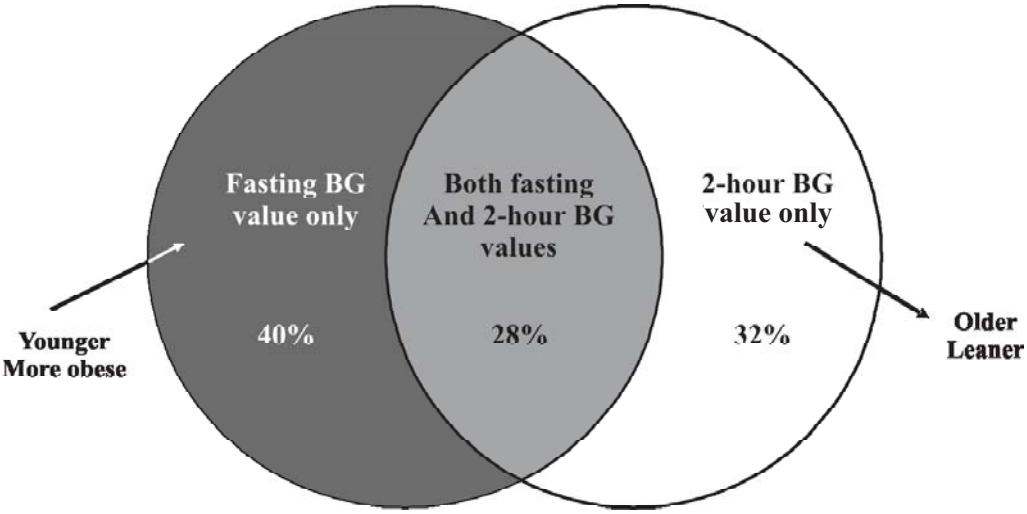
Diagnosis

The diagnosis of diabetes in an asymptomatic individual should never be made on the basis of a single abnormal glucose value. Verification of the diagnosis with repeat testing is required, unless an individual presents with unequivocal hyperglycaemia along with its classic symptoms. The diagnostic values for diabetes mellitus and other categories of hyperglycaemia are shown in Table 4.

Using fasting plasma glucose may not be equivalent to or as accurate as the use of an oral glucose tolerance test (OGTT) in identifying individuals with diabetes. Data from the

Table 4. Diagnostic values for diabetes mellitus and other categories of hyperglycaemia [21]

	Venous plasma glucose concentration	
	mmol/L	mg/dL
Diabetes mellitus		
fasting **or**	≥7.0	≥126
2-hour post-75 g glucose load	≥11.1	≥200
IGT		
fasting (if measured) **and**	<7.0	<126
2-hour post-75 g glucose load	≥7.8 and <11.1	≥140 and <200
IFG		
fasting **and** (if measured)	≥5.6 and <7.0	≥100 and <126
2-hour post-75 g glucose load	<7.8	<140



BG: blood glucose

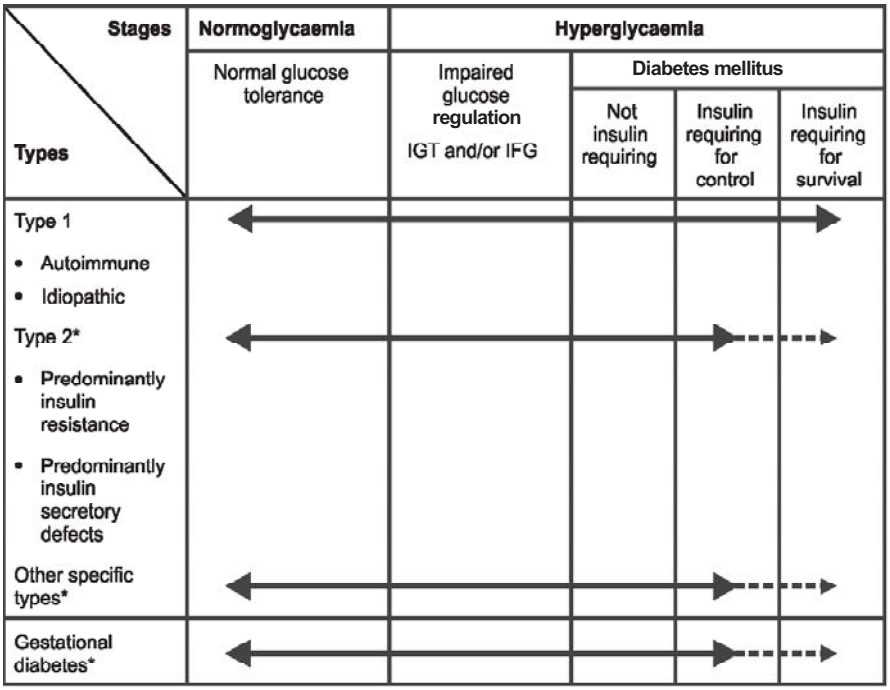
Figure 1. Fasting and 2-hour glucose values identify different persons with diabetes [21]

European DECODE study (Figure 1) show that about one-third of people with diabetes have elevated fasting glucose values but have 2-hour post-load glucose values below the diabetic range, and vice versa. Also, patients diagnosed with diabetes based solely on the fasting glucose level tend to have a different phenotype from those identified based solely on the 2-hour OGTT glucose value [2,21,22].

Classification

The classification of diabetes mellitus has evolved considerably over time, taking into account recent advances in the diabetes field. The classification is now primarily based on the etiology (causes) of the disease, rather than its treatment (Figure 2). The revised classification encompasses both clinical stages and etiological types of hyperglycaemia and results from improved understanding of the causes of diabetes mellitus [21].

The clinical staging reflects that diabetes mellitus, regardless of its etiology, progresses through several clinical stages during its natural history. Individuals can move from one stage to another in either direction [21]. The severity of glycaemia may change over time depending on the extent of the underlying disease processes. While there are autoimmune markers that help identify type 1 diabetes mellitus, there are few sensitive or highly specific indicators of the type 2 process at present, although these are likely to be revealed in the future. The same disease process leading to type 2 diabetes mellitus can



* In rare instances patients in these categories (e.g. Vector toxicity, Type 1 presenting in pregnancy, etc.) may require insulin for survival.

Figure 2. Disorders of glycaemia: etiological types and clinical stages [21]

cause impaired fasting glycaemia and/or impaired glucose tolerance without fulfilling the criteria for the diagnosis of diabetes mellitus. In some individuals with type 2 diabetes, adequate glycaemic control can be achieved with weight reduction, exercise and/or oral agents. These individuals, therefore, do not require insulin and may even revert to IGT or normoglycaemia. Other individuals require insulin for adequate glycaemic control but can survive without it. These individuals, by definition, have some residual insulin secretion. Individuals with extensive ß-cell destruction, and therefore no residual insulin secretion, require insulin for survival. The severity of the metabolic abnormality can even regress (e.g. with weight reduction), progress (e.g. with weight gain), or stay the same [21].

Terminology

There are two main types of diabetes: type 1 (requiring insulin for survival) and type 2 (may or may not require insulin for metabolic control). It is recommended that the terms insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus, and their acronyms IDDM and NIDDM, no longer be used. These terms are confusing and frequently result in patients being classified on the basis of treatment rather than etiology.

Type 1 diabetes mellitus encompasses the majority of cases, which are primarily due to pancreatic islet ß-cell destruction and are prone to ketoacidosis. Type 1 includes those cases attributable to an autoimmune process, as well as those with ß-cell destruction for which neither etiology nor pathogenesis is known (idiopathic). It does not include those forms of ß-cell destruction or failure to which specific causes can be assigned (e.g. cystic fibrosis, mitochondrial defect, etc.) [1,2,21,23].

Type 2 includes the common major form of diabetes mellitus which results from defect(s) in insulin secretion, almost always with a major contribution from insulin resistance. It has been argued that a lean phenotype 2 diabetes mellitus in adults found in the Indian sub-continent may be very distinct from the more characteristic form of type 2 found in Caucasians. Not enough information is available, however, to characterize such subjects separately [21].

A recent international meeting reviewed the evidence for, and characteristics of, diabetes mellitus in under-nourished individuals. While it appears that malnutrition may influence the expression of several types of diabetes, the evidence that diabetes can be caused by malnutrition or protein deficiency per se is not convincing. Therefore, it was recommended that the class 'malnutrition-related diabetes' (MRDM) be deleted. The former subtypes of MRDM, protein-deficient pancreatic diabetes (PDPD or PDDM), may be considered as a malnutrition-modulated or -modified form of diabetes mellitus for which more studies are needed. The other former sub-type of MRDM, fibrocalculous pancreatic diabetes (FCPD), is now classified as a disease of the exocrine pancreas, fibrocalculous pancreatopathy, which may lead to diabetes mellitus. The class impaired glucose regulation (IGT) is classified as a stage of impaired glucose regulation, since it can be observed in any hyperglycaemic disorder, and is itself not diabetes. A clinical stage of IFG was introduced to classify individuals who have fasting glucose values above the normal range, but below that diagnostic of diabetes. The term gestational diabetes was retained, but now encompasses the groups formerly classified as gestational impaired glucose tolerance (GIGT) and gestational diabetes mellitus (GDM) [21,22].

Impaired glucose regulation

IGT and/or impaired fasting glycaemia (IFG) refer to a stage that is intermediate between normoglycaemia and diabetes and they represent risk categories for future development of diabetes mellitus [21,23]. The risk of diabetes is increased in persons with IGT. About one third of IGT subjects develop type 2 diabetes mellitus, and the annual incidence rate ranges from 2% to 10% per year [21,22] depending on the population and major risk factors. In addition, the prevalence of electrocardiogram (ECG) abnormalities is significantly higher in persons with IGT compared to persons with normal glucose tolerance, and cardiovascular mortality is higher [23]. Although there are no published estimates of the overall worldwide prevalence of IGT, it is thought to be higher than that of diabetes at around 200 million persons. Therefore, any decision on screening and

intervention has a big implication on resources, as it more than doubles the population eligible for intervention [1,2,23].

The relationship between the prevalence of diabetes and IGT in the population is not simple, but some authors have proposed the use of an epidemicity index [21,22]. This is the ratio between IGT prevalence and diabetes mellitus prevalence, and might indicate the potential for future increase in type 2 prevalence. A high epidemicity index indicates the beginning of an epidemic and is mostly seen in developing countries. Therefore, it is a big issue for developing countries whether to do something about IGT. The values for IFG are a fasting plasma glucose concentration of ≥6.1 mmol/L (110 mg/dL) (whole blood 5.6 mmol/L, 100 mg/dL), but <7.0 mmol/L (126 mg/dL) (whole blood 6.1 mmol/L, 110 mg/dL). If an OGTT is performed, some individuals with IFG will have IGT. If resources allow, WHO recommends that all those with IFG have an OGTT to exclude the diagnosis of diabetes.

Individuals who meet criteria for IGT or IFG may be euglycaemic in their daily lives as shown by normal or near-normal glycated haemoglobin levels. IGT and IFG are not clinical entities in their own right, but rather risk categories for future diabetes and/or cardiovascular disease. They can occur as an intermediate stage in any of the disease processes. IGT is often associated with the metabolic syndrome (insulin resistance syndrome). IGT may not be directly involved in the pathogenesis of cardiovascular disease, but rather may serve as an indicator or marker of enhanced risk by virtue of its correlation with the other elements of the metabolic syndrome. Self-evidently, those individuals with IGT manifest glucose intolerance only when challenged with an oral glucose load.

Normoglycaemia

A fasting venous plasma glucose concentration of <6.1 mmol/L (110 mg/dL) has been chosen as “normal”. Although this choice is arbitrary, such values have been observed in people with proven normal glucose tolerance; however, others with fasting glucose values <6.1 mmol/L may have IGT if an OGTT is performed. Fasting glucose values above this level are associated with a progressively greater risk of developing microvascular and macrovascular complications.

In addition, the pathological or etiological process that often leads to diabetes mellitus begins, and may be recognizable, in some subjects who have normal glucose tolerance. Recognition of these processes at any early stage may be useful if progression to more advanced phases can be prevented. Conversely, effective treatment, or occasionally the natural history of some forms of diabetes mellitus, may result in reversal of hyperglycaemia to a state of normoglycaemia [21–23].

Etiological types

Etiological types designate defects, disorders or processes that often result in diabetes mellitus.

Type 1 diabetes mellitus

Type 1 indicates the processes of ß-cell destruction that may ultimately lead to diabetes mellitus in which insulin is required for survival to prevent the development of ketoacidosis, coma and death. An individual with a type 1 process may be metabolically normal before the disease is clinically manifest, but the process of ß-cell destruction can be detected. Type 1 is usually characterized by the presence of anti-glutamic acid decarboxylase (anti-GAD) antibodies, islet cell or insulin antibodies which identify the autoimmune processes that lead to ß-cell destruction. In some subjects with this clinical form of diabetes, particularly non-Caucasians, no evidence of an autoimmune disorder is demonstrable and these are classified idiopathic type 1. Etiological classification may be possible in some circumstances and not in others. Thus, the category of type 1 diabetes can be identified if appropriate antibody determinations are performed. It is recognized that such measurements may be available only in certain centres at present [23].

Type 2 diabetes mellitus

Type 2 is the most common form of diabetes and is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that this form of diabetes is clinically manifest. The specific reasons for the development of these abnormalities are not yet known [23].

Ketoacidosis is very rare in type 2 diabetes. The insulin resistance that occurs in this type is partly explained by the obesity that often coexists with the disease.

Other specific types [21–23]

Other specific types are currently less common causes of diabetes mellitus, but are conditions in which the underlying defect or disease process can be identified in a relatively specific manner.

They include:

- genetic defects in ß-cells, such as maturity-onset diabetes of the young;
- genetic defects in insulin action, such as Leprechaunism;
- diseases of the exocrine pancreas, such as cancer of the pancreas, cystic fibrosis and fibrocalculous pancreatopathy (a form of diabetes, which was formerly classified as one type of malnutrition-related diabetes mellitus);
- endocrinopathies, such as Cushing syndrome, acromegaly and phaeochromocytoma;
- drugs or chemicals, such as steroids and thiazides;

- infections, such as rubella;
- uncommon forms of immune-related diabetes, such as the type associated with insulin-receptor antibodies;
- other rare genetic syndromes associated with diabetes, such as Klinefelter syndrome and Down syndrome.

Chapter 3

Diabetes mellitus in special groups and circumstances

Children and adolescents [21]

While type 2 diabetes mellitus used to be almost non-existent in children, its prevalence has been increasing rapidly over the past two decades, mostly because of the rapid increase in childhood obesity. A recent study from Taiwan showed type 2 to be the leading cause of diabetes in children aged 6–18 years.

In the Eastern Mediterranean Region type 2 diabetes should be screened for in children aged over 10 years if the child is overweight (>120% of the ideal body weight) and if two of the following characteristics are present:

- positive family history of type 2 diabetes mellitus (first- or second-degree relative);
- Arab ethnicity;
- signs associated with insulin resistance (polycystic ovarian syndrome, hypertension, dyslipidaemia).

Testing should be repeated every two years in children at risk.

Gestational diabetes

Background

Gestational diabetes is a state of carbohydrate intolerance resulting in hyperglycaemia of variable severity, with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has previously gone unrecognized. The definition applies irrespective of whether or not insulin is used for treatment or whether the condition persists after pregnancy [21,23]. Women who are known to have diabetes mellitus and who subsequently become pregnant do not have gestational diabetes but have "diabetes mellitus and pregnancy" and should be treated accordingly before, during and after the pregnancy.

In the early part of pregnancy (e.g. first trimester and half of second trimester) fasting and postprandial glucose concentrations are normally lower than in normal, non-pregnant women. Elevated fasting or postprandial plasma glucose levels may well reflect

the presence of diabetes that antedates pregnancy, but criteria for designating abnormally high glucose concentration at this time in pregnancy have not yet been established. The occurrence of higher than usual plasma glucose levels at this time in pregnancy mandates careful management and may be an indication for carrying out an OGTT. Nevertheless, normal glucose tolerance in the early part of pregnancy does not itself establish that gestational diabetes will not develop later.

Individuals at high risk for gestational diabetes include:

- older women;
- obese women;
- those with previous history of glucose intolerance;
- any pregnant woman who has elevated fasting, or casual, blood glucose levels;
- those with a history of gestational diabetes mellitus;
- those with a history of large-for-gestational-age babies;
- women from certain high risk ethnic groups;
- strong family history of diabetes mellitus [23].

It may be appropriate to screen pregnant women belonging to high-risk population groups during the first trimester of pregnancy in order to detect previously undiagnosed diabetes mellitus. Women at high risk who screen negatively and average risk women should be tested between 24 and 28 weeks of gestation [23].

Diagnosis of gestational diabetes

To determine if gestational diabetes is present in pregnant women, a standard OGTT should be performed after overnight fasting (8–14 hours) by giving 75 g anhydrous glucose in 250–300 mL water. Plasma glucose is measured fasting and then after 2 hours. Pregnant women who meet WHO criteria for diabetes mellitus or IGT are classified as having gestational diabetes (Box 1). After the pregnancy ends, the woman should be reclassified as having either diabetes mellitus, IGT or normal glucose tolerance based on the results of a 75 g OGTT, 6 weeks or more after delivery. It should be emphasized that such women, regardless of the 6-week post-pregnancy result, are at increased risk of subsequently developing diabetes. The significance of IFG in pregnancy remains to be established. Any woman with IFG, however, should have a 75 g OGTT [21,23]. Alternatively, the 100 g OGTT may be substituted for the 75 g OGTT in screening for gestational diabetes mellitus.

Box 1. Diagnostic criteria for gestational diabetes [21,23]

75 g OGTT with two or more positive values

fasting ≥95 mg/dL (5.3 mmol/L)

1 hour ≥180 mg/dL (10 mmol/L)

2 hours ≥155 mg/dL (8.6 mmol/L)

100 g OGTT with two or more positive values

fasting ≥95 mg/dL (5.3 mmol/L)

1 hour ≥180 mg/dL (10 mmol/L)

2 hours ≥155 mg/dL (8.6 mmol/L)

3 hours ≥140 mg/dL (7.8 mmol/L)

or

50 g GCT with blood glucose value after 1 hour

≥130 mg/dL (7.2 mmol/L), then confirm with 75 g or 100 g OGTT

OGTT, oral glucose tolerance test; GCT, glucose challenge test

Metabolic syndrome

Often a person with abnormal glucose tolerance (IGT or diabetes) will be found to have at least one or more of the other cardiovascular disease risk factors such as hypertension, central (upper body) obesity, and dyslipidaemia. This clustering has been labelled diversely as the metabolic syndrome, syndrome X, or the insulin resistance syndrome [21]. Epidemiological studies confirm that this syndrome occurs commonly in a wide variety of ethnic groups including Caucasians, Afro-Americans, Mexican-Americans, Asian Indians, Chinese, Australian Aborigines, Polynesians and Micronesians. In 1988, Dr Gerald Reaven focused attention on this cluster, naming it Syndrome X. Central obesity was not included in the original description, so the term metabolic syndrome is now favoured. Alone, each component of the cluster conveys increased cardiovascular disease risk, but as a combination they become much more powerful. This means that the management of persons with hyperglycaemia and other features of the metabolic syndrome should focus not only on blood glucose control but also include strategies to reduce the impact of other cardiovascular disease risk factors.

The metabolic syndrome with normal glucose tolerance identifies the subject as a member of a group at very high risk of future diabetes. Thus, vigorous early management of the syndrome may have a significant impact on the prevention of both diabetes and cardiovascular disease, especially as it is well documented that the features of the metabolic syndrome can be present for up to 10 years before glycaemic disorder is detected.

Table 5. Diagnostic criteria for the metabolic syndrome

Criteria	Defining level
Abdominal obesity	
Men	Waist circumference >102 cm (>40 inches)
Women	Waist circumference >88 cm (>35 inches)
High levels of triglycerides	At least 150 mg/dL
Low HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
High blood pressure	At least 130/>85 mmHg
High fasting glucose	At least 110 mg/dL

HDL: high-density lipid

Diagnosis of metabolic syndrome

At least three of the five criteria shown in Table 5 must be met to diagnose metabolic syndrome.

Several other components of the metabolic syndrome have been described (e.g. hyperuricaemia, coagulation disorders) but are not considered criteria for its diagnosis.

Hypertension

Background

Macrovascular disease constitutes the major cause of diabetes mortality, with 80% of patients having and/or dying of cardiovascular, cerebrovascular or peripheral arterial disease. Patients with diabetes mellitus exhibit a two to four-fold increase in the risk of coronary events compared to non-diabetic individuals.

Although large-scale studies have shown a clear association between improvement in glycaemic control and reduction in microvascular end-organ damage (retinopathy, nephropathy and neuropathy), they have not been able to show a consistent similar relationship between glycaemic control and macrovascular complications. However, many trials have shown a benefit with respect to cardiovascular events, morbidity and mortality when co-existent hypertension is treated. In addition, control of hypertension is also beneficial to microvascular complications. This issue is of paramount importance since close to 60% of patients with diabetes are known to have hypertension. Therefore aggressive strategies aimed at identifying and treating high blood pressure in patients with diabetes should lead to substantial reduction in the risk of cardiovascular morbidity and mortality.

Table 6. Classification of blood pressure for adults aged ≥18 years

BP classification	SBP (mmHg)		DBP (mmHg)
Normal	<120	and	<80
Pre-hypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

SBP: systolic blood pressure, DBP: diastolic blood pressure

It is important to emphasize that hypertension is but one element of the metabolic syndrome in patients with type 2 diabetes mellitus, and therefore due attention should be given to other coexisting cardiovascular risk factors (such as obesity and dyslipidaemia), and appropriate management of these conditions should be instituted.

Definition of hypertension

Hypertension refers to elevated blood pressure. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, 2003 [24]:

- hypertension is defined as a blood pressure ≥140/90 mmHg.
- prehypertension refers to systolic blood pressure 120–139 mmHg or diastolic blood pressure 80–89 mmHg.
- normal blood pressure is <120/80 mmHg.

The classification of blood pressure for adults aged ≥18 years is shown in Table 6. Diagnosis should be made based on the mean of two or more blood pressure measurements made while the patient is in the seated position. The possibility of secondary hypertension should be kept in mind and appropriate laboratory investigation undertaken as indicated.

Risks associated with hypertension

People with diabetes and hypertension have a two-fold increased risk of cardiovascular mortality compared to patients with diabetes alone. In addition, they have an increased risk of retinopathy and nephropathy. Lowering the blood pressure has been shown to have a beneficial effect on these complications. Each 10 mmHg decrease in systolic blood pressure leads to a decrease in diabetes-related mortality by 15%, diabetes-related complications by 12%, and myocardial infarctions by 11%.

It is now well established that multiple metabolic abnormalities associated with insulin resistance and increased cardiovascular risk such as dyslipidaemia, obesity and

hypertension are already present at diagnosis. Consequently, treatment of hyperglycaemia alone cannot be expected to normalize the two to four-fold increase risk of cardiovascular mortality of these patients. In keeping with this, results of many intervention studies have demonstrated marked benefit from antihypertensive, lipid-lowering and antiplatelet therapy. Earlier recognition of at-risk individuals with screening and the subsequent investigation of a wide spectrum of preventive and corrective measures are recommended.

Blood pressure goal

There is no threshold for the risk of cardiovascular disease, but rather a continuous decrease in risk as blood pressure is reduced. The Hypertension Optimal Treatment (HOT) trial, the United Kingdom Prospective Diabetes Study (UKPDS), and the Appropriate Blood Pressure Control in Diabetes (ABCD) study showed a consistent positive effect cardiovascular events or mortality when blood pressure is reduced. Based on the above trials and on recommendations from international organizations, it is now accepted that the goal blood pressure level in diabetes mellitus should be <130/80 mmHg.

Screening for hypertension

For screening purposes, the following guidelines are recommended:

- patients should have their blood pressure checked at each clinic visit;
- orthostatic measurements are indicated if autonomic neuropathy is suspected;
- if blood pressure is found to be ≥130/80 mmHg, it should be repeated on a separate visit day;
- if the diagnosis is confirmed, treatment may be started.

Dyslipidaemia

Characteristics of diabetic dyslipidaemia

Diabetic dyslipidaemia is characterized by:

- elevated triglycerides;
- low high-density lipoprotein (HDL) cholesterol;
- shift in low-density lipoprotein (LDL) particle density towards small, dense LDL (type B);
- tendency towards postprandial lipaemia.

Triglycerides are considered to have atherogenic properties. HDL is considered a protective lipoprotein because it contributes to reverse cholesterol transport. Small,

dense LDL is considered more atherogenic than large, buoyant LDL because it is more prone to oxidation and can trigger inflammatory processes.

Classification

Tables 7–10 classify the levels of total, LDL and HDL cholesterol and triglycerides.

Table 7. LDL cholesterol classification

LDL-cholesterol (mmol/L)	LDL cholesterol (mg/dL)	Classification
<2.58	<100	Optimal
2.58–3.33	100–129	Near or above optimal
3.36–4.11	130–159	Borderline high
4.13–4.88	160–189	High
≥4.91	≥190	Very high

Table 8. Total cholesterol classification

Total cholesterol (mmol/L)	Total cholesterol (mg/dL)	Classification
<5.17	<200	Desirable
5.17–6.18	200–239	Borderline high
≥6.20	≥240	High

Table 9. HDL cholesterol classification

HDL cholesterol (mmol/L)	HDL cholesterol (mg/dL)	Classification
<1.03	<40	Low
≥1.55	≥60	High

Table 10. Triglycerides classification

Triglycerides (mmol/L)	Triglycerides (mg/dL)	Classification
<1.69	<150	Optimal
1.69–2.25	150–199	Borderline high
2.26–5.63	200–499	High
≥5.64	≥500	Very high

Screening for diabetic dyslipidaemia

A fasting lipid profile is recommended on a yearly basis for patients with diabetes. The frequency may be decreased to every other year for patients with optimal lipid levels. A lipid profile should include measurement of total cholesterol, HDL cholesterol and triglycerides. LDL cholesterol can be calculated as long as triglycerides are below 400 mg/dL, using the formula:

LDL cholesterol = total cholesterol – HDL cholesterol – [$^1/_5$ × triglycerides].

Otherwise serum LDL cholesterol may need to be measured directly.

Screening is important in order to identify patients with suboptimal lipid profiles and institute corrective measures for either primary or secondary prevention.

If elevated LDL cholesterol or triglycerides are found, clinical and laboratory assessment should be performed in order to rule out secondary causes of dyslipidaemia, such as:

- hypothyroidism (symptoms, check thyroid-stimulating hormone)
- obstructive liver disease (liver function tests)
- chronic renal disease (renal function tests, creatinine clearance, urinalysis)
- drugs (estrogen, progestins, corticosteroids, thiazides)
- alcohol (raises triglycerides).

Brittle diabetes [23]

Brittle diabetes refers to patients with type 1 diabetes mellitus who exhibit wide and severe fluctuations in blood glucose despite efforts to modify and adjust their daily activities, meal planning and insulin regimen. They have common occurrences of hypoglycaemia, frequently severe hyperglycaemia and episodes of diabetic ketoacidosis. Treatment of patients in this category has been a frustration for most health-care providers. The cause of the brittleness is unclear, but may be due to a combination of psychosocial, lifestyle, neurohumoral and hormonal abnormalities. It can occur in type 2 patients requiring insulin, but this is rare [25].

Chapter 4

Screening for diabetes mellitus

Background

The question of mass community screening for diabetes remains controversial. The underlying philosophy of screening has been that detection of diabetes in asymptomatic or minimally symptomatic individuals will result in effective treatment that may retard its progression and reduce the risk or the severity of complications, thus diminishing premature morbidity and mortality. This is brought into focus by the frequent presence of specific complications at the time of clinical diagnosis and the estimate that on average subjects had had type 2 diabetes mellitus for 4–7 years prior to diagnosis [21,23].

Over the years, opinions have changed frequently on the value of mass screening. Initially it was widely recommended, however at present it is recommended only for individuals at risk or for epidemiological studies. This position is supported by many well-designed screening programmes that have provided valuable information about the prevalence of diabetes and IGT and their natural history in different populations. Such data are essential for public health planning and provide information for continued evaluation of the current diagnostic criteria. Screening programmes can also improve community awareness and pave the way for education about diabetes.

Important considerations in the design of an appropriate screening programme include [21,23]:

- the sensitivity, specificity and predictive value of the screening test;
- the cost-effectiveness and resource requirements of the screening methodology and any necessary follow-up in the context of the anticipated positive detection rate;
- the definition of the target population to be screened;
- the provision of adequate and effective follow-up and care for individuals having positive test results.

There are however potential adverse effects of screening:

- psychological stress, socioeconomic disadvantage and additional costs resulting from a false-positive test result;
- false reassurance of a false-negative test result;
- medical complications of the screening test and the need for follow-up of positive screenees;

- medical complications of the intervention in people diagnosed as having diabetes can prove costly.

Therefore appropriate explanations and procedures should be incorporated into the screening protocol and programme design to minimize adverse effects and to address them when they do occur. It must be emphasized that screening is only worthwhile if an effective intervention can be introduced to decrease the burden of the disease or prevent its complications. The current state of knowledge suggests that definitive proof of the value of screening is lacking, but evidence in its favour is steadily accumulating. The approach to screening that is adopted will depend on:

- the resources available;
- the potential disease burden;
- the risk factor distribution [1,2,21,22].

Screening approaches

A positive result in a screening test indicates only a high probability of the individual having the disease. The diagnosis of diabetes cannot be made on the basis of a single abnormal blood glucose value in an asymptomatic individual [21]. Confirmatory tests are always necessary for a definitive diagnosis to be made. There are three different approaches to screening: population, selective and opportunistic.

Population screening [21]

Population screening is worthwhile only for health care planning, for epidemiological research purposes or in high-prevalence populations. It can be used to identify individuals with IGT provided the OGTT is employed. In most societies, it is ineffective in terms of cost and effort to screen low-risk individuals for type 2 diabetes mellitus, such as children and young adults.

Selective screening [21]

Selective screening is undertaken in groups known to have risk factors for developing type 2 diabetes mellitus. In low-prevalence communities, an even more selective approach should be adopted.

Opportunistic screening

Opportunistic screening occurs when high-risk individuals present themselves to some sector of the health care system. It is the most employed method and is highly cost-effective in that no resources are needed to organize the screening or call for subjects [21].

Screening tools

Glucose measurement [21]

At present there is no satisfactory substitute to glucose measurement. Alternatives, such as measurements of glycated haemoglobin, glycated proteins and 1,5-anhydroglucitol, although specific, are too insensitive to reliably detect lesser degrees of glycaemic disturbances. There are many methods available for measuring blood glucose, ranging from visually-read test-strips to sophisticated automated methods. Precision and accuracy are required for screening. If portable meters are to be used, they should be checked under a full quality assurance programme and a coefficient of variation >5% should not be accepted. When automated procedures are used, care must be taken to minimize the risk of errors in sample identification.

Oral glucose tolerance test (OGGT)

The oral glucose tolerance test remains the definitive confirmatory diagnostic test for diabetes mellitus. Glucose levels ≥11.1 mmol/L (200 mg/dL) 2 hours after a 75 g oral glucose load are diagnostic of diabetes.

Fasting plasma glucose

Fasting is defined as avoiding the consumption of any food or beverage other than water for at least 10–16 hours before testing. Fasting blood and plasma glucose levels are interpreted in Table 11.

Casual blood glucose measurement

Levels >7.8 mmol/L should be an indication for further testing. A value equal to 10.0 mmol/L in venous whole blood or 11.1 mmol/L in venous plasma is suggestive of diabetes. Sensitivity and specificity can vary, depending on the cut-off used [23].

Table 11. Interpretation of fasting blood and plasma glucose levels [21–23]

Fasting plasma glucose	Interpretation
<5.6 mmol/L (<100 mg/dL)	Excludes diabetes (probably)
5.6–6.0 mmol/L (100–109 mg/dL)	Low probability, may be an indication for diagnostic testing among high-risk individuals (OGTT)
6.1–6.9 mmol/L (110–125 mg/dL)	Indication for diagnostic testing (OGTT)
≥7.0 mmol/L (≥126 mg/dL)	Indicates diabetes, confirmation with repeat testing required

OGTT: oral glucose tolerance test

Table 12. Summary of screening methods for diabetes mellitus [21]

Diabetes type	Method	Specificity	Sensitivity	Cost
Type 2	Glycated HbA1c or proteins	+ + +	+/–	+ + +
	Urine glucose	+ + +	+/–	+
	Casual blood glucose	+ +	+	+
	Fasting blood glucose	+ + +	+	+
	OGTT	+ + +	+ + +	+ +
Type 1	HLA type	+/–	–	+ + +
	ICA	+	+	+ + +
	Anti-GAD	+	+	+ + +
	Early insulin secretion	+/–	+	+ +

–: none
+/–: none or minimal
+: low
+ +: intermediate
+ + +: high
HLA: human leukocyte antigen
ICA: islet-cell cytoplasmic antibodies
Anti-GAD: antibodies to glutamic acid decarboxylase

Urine glucose measurement

Urine glucose measurement is insensitive, but relatively specific, for the detection of diabetes. It may be used if reliable blood glucose measurements are not available. Sensitivity is improved by using postprandial urine samples. A positive urine test result indicates the need for confirmatory blood glucose testing [22].

A summary of the screening methods for diabetes mellitus is given in Table 12.

Screening strategies

Screening programmes should not be embarked upon without full recognition of the cost implications, both for screening and for follow-up and clinical care of individuals in whom diabetes is detected. Proper training is required for those conducting the screening, and the importance and relevance of the diagnostic programme to health care should be made explicit. Every screening programme must have an established mechanism for follow-up and further evaluation of those with a positive result.

To be more specific, a screening programme should identify individuals with one or more diabetes risk factors. This can be done by means of a written or verbal questionnaire. Individuals with more than one risk factor should be referred for evaluation and testing.

Screening for type 1 diabetes mellitus [23]

Given current knowledge, screening can be recommended only for research purposes related to the prevention of type 1 diabetes mellitus. Different screening approaches can

be applied depending on the particular research question. The four parameters available for use are:

- family history;
- genetic markers (human leukocyte antigens);
- immunological risk markers, e.g. islet-cell cytoplasmic antibodies, insulin auto-antibodies and antibodies to glutamate decarboxylase;
- metabolic risk markers: screening for pre-symptomatic type 1 diabetes mellitus and individuals at risk remains purely experimental at this time, but there is intense research activity in this area.

Screening for type 2 diabetes mellitus [23,25]

The main reasons for the current interest in screening for type 2 diabetes are:

- there is a long, latent, asymptomatic period in which the condition can be detected;
- a substantial proportion of people with type 2 diabetes are undiagnosed;
- a substantial proportion of newly referred cases of type 2 diabetes already have evidence of the micro-vascular complications of dibaetes;
- the rising prevalence of type 2 diabetes in the Eastern Mediterranean Region;
- the seriousness of the immediate effects and long-term complications of type 2 diabetes;
- evidence supporting the efficacy of intensive blood glucose control, blood pressure control and blood lipid control in type 2 diabetes; and
- accumulating evidence that treatment of hypertension dylipidaemia can prevent cardiovascular disease in people with type 2 diabetes [26].

Screening of asymptomatic adults for type 2 diabetes mellitus should be done in the following groups, and if normal should be repeated every three years. High-risk characteristics include:

- ethnicity: certain groups such as Pacific Islanders, Australian Aborigines, Mauritian, migrant Asian Indians and Chinese, and Indigenous Americans show high diabetes prevalence. Recently, Arab ethnicity was designated as a risk factor for type 2 diabetes (Rubeean K, personal communication, 2004);
- individuals aged ≥35 years;
- overweight (body mass index ≥25 kg/m^2);
- first-degree relative with type 2 diabetes;
- women with previous history of gestational diabetes mellitus or who delivered a baby weighing >4 kg;

- individuals diagnosed previously with IFG or IGT;
- hypertensive individuals with blood pressure >140/90 mmHg;
- HDL cholesterol level ≤0.9 mmol/L (35 mg/dL) and/or triglyceride level >2.82 mmol/L (250 mg/dL);
- other medical conditions associated with insulin resistance like polycystic ovarian syndrome or acanthosis nigricans;
- history of vascular disease.

Evaluation [23]

Screening for diabetes is justified on the grounds that early detection allows effective early intervention, thus diminishing the likelihood of the development of complications. Selective high-risk and opportunistic screening must be accompanied by confirmatory diagnosis and appropriate follow-up of new cases. Screening for IGT may be justified in high-risk populations but requires an OGTT for identification and a lifestyle intervention programme.

Screening programmes should, therefore, be evaluated in terms of:

- numbers of new cases detected;
- cost per new case detected;
- actions taken for individuals with positive test results;
- long-term benefits of early detection.

Chapter 5

Management of diabetes mellitus

Background

Diabetes mellitus should not be managed based on symptoms alone. Glycaemic goals are based on evidence of what glucose levels constitute a risk for developing complications. It is, however, inappropriate to aggressively approach target glucose levels when it may adversely affect the patient. Treatment goals must, therefore, be individualized.

The goal of treatment of diabetes mellitus is to control blood glucose and ultimately prevent long-term complications, as shown by major diabetes studies like the United Kingdom Prospective Diabetes Study group and Diabetes Control and Complications Trial [27–29]. Insulin therapy is necessary to control hyperglycaemia in type 1 diabetes mellitus. Provided hyperglycaemia is mild in type 2 diabetes, patients may be given at least a one month trial of diet, exercise and weight management in order to control hyperglycaemia. If this regimen does not lead to adequate blood glucose control, the physician will need to prescribe oral anti-hyperglycaemic agents and/or insulin [29].

Objectives of therapy

The main objectives of therapy for diabetes mellitus are:

- to eliminate symptoms of hyperglycaemia;
- to achieve optimum control;
- to reduce or eliminate microvascular and macrovascular complications of diabetes mellitus;
- to treat associated disorders;
- to allow the patient to achieve as normal a lifestyle as possible.

Therapy targets

The markers for diabetes mellitus control are blood glucose and HbA_{1c}. The recommended goals are shown in Table 13.

HbA_{1c} should be measured regularly in every patient (at three month intervals). Levels of HbA_{1c} can be falsely altered (increased or decreased) in patients with

Table 13. Optimal control indicators for management of diabetes mellitus [21,23,27–29]

Glycaemic control indicator	Normal	Target	Action needed
Plasma values			
Pre-meal glucose, mg/dL	<110	90–130	<90 or >150
mmol/L	<6.1	5.0–7.2	<5.0 or >8.3
Bedtime glucose, mg/dL	<120	110–150	<110 or >180
mmol/L	<6.7	6.1–8.3	<6.1 or >10.0
Whole blood values			
Pre-meal glucose, mg/dL	<100	80–120	<80 or >140
mmol/L	<5.5	4.4–6.7	<4.4 or >7.8
Bedtime glucose, mg/dL	<110	100–140	<100 or >160
mmol/L	<6.1	5.5–7.8	<5.5 or >8.9
HbA_{1c} (%)	<6.0	<7.0	>8.0

Self-monitoring of blood glucose (SMBG) should be available for all diagnosed with diabetes, as an integral part of self-management education.

haemoglobinopathies. Fructosamine is not an adequate substitute for HbA_{1c}, but fulfils some of the same functions. It may be used when there is coexisting haemoglobin abnormalities falsely affecting the level of HbA_{1c} (i.e. thalassemia), and during pregnancy for early detection of deteriorations in glycaemic control [23].

It is now well established that multiple metabolic abnormalities associated with insulin resistance and increased cardiovascular risk, such as dyslipidaemia, obesity and hypertension, are already present at diagnosis. Consequently, treatment of hyperglycaemia alone cannot be expected to normalize the two to four-fold increased risk of cardiovascular mortality of these patients. In align with this, results of many intervention studies have demonstrated marked benefit from antihypertensive, lipid-lowering and anti-platelet therapy. Earlier recognition of at-risk individuals with screening and the subsequent investigation of a wide spectrum of preventive and corrective measures is recommended. Table 14 shows the recommendations for metabolic and non-metabolic targets (lipid profile, body mass index, blood pressure) for diabetic patients.

There is a slight difference between the self-monitoring of blood glucose results and the result of plasma laboratory measurement of plasma glucose (laboratory plasma glucose is usually 10%–15% higher), unless self-monitoring blood glucose values are adjusted to plasma glucose.

Table 14. Recommendations for metabolic and non-metabolic targets [21,23,27,29]

	Good	Borderline	Poor
Total cholesterol, mg/dL (mmol/L)	<200 (5.2)	200–250 (5.2–6.5)	>250 (6.5)
Fasting triglycerides, mg/dL (mmol/L)	<150 (1.7)	150–200 (1.7–2.2)	>200 (2.2)
HDL-cholesterol, mg/dL (mmol/L)			
male	>45 (1.15)	35–45 (0.9–1.15)	<35 (0.9)
female	>55 (1.40)	45–55 (1.15–1.40)	<45 (1.15)
LDL cholesterol mg/dL (mmol/L)	<100 (2.56)	100–130 (2.56–3.33)	>130 (3.33)
Total cholesterol/HDL ratio			
male	<6.4	–	–
female	<5.6	–	–
Body mass index (kg/m^2)			
male	<25.0	25.0–27.0	>27.0
female	<24.0	24.0–26.0	>26.0
Blood pressure (mmHg)	<130/80	–	–

LDL: low-density lipid HDL: high density lipid

Components of the clinic visit

Each patient visit to the health care facility should cover the following items.

- Medical history, including:
  - symptoms of hyperglycaemia or hypoglycaemia
  - results of prior HbA_{1c} and home blood glucose records
  - meal patterns including frequency and content, and any change in weight
  - lifestyle and psychosocial elements
  - any acute complications such as infection, hypoglycaemia or ketoacidosis
  - any chronic complications related to vision, kidney, nerve, or the cardiovascular system
  - any associated cardiovascular risk factors such as a positive family history, hypertension, dyslipidaemia
  - review of all medications, ask if the patient is taking aspirin
- Physical examination, including:
  - height and weight
  - vital signs, including blood pressure supine and sitting
  - fundoscopic examination, looking for any signs of retinopathy
  - oral examination, including gums

  - cardiovascular including evaluation for pulses and bruits
  - abdominal exam, assess liver size
  - foot examination, for deformities
  - neurological examination: light, touch, vibration sense, reflexes, motor strength.
- Diagnostic studies, including:
  - fasting and 2-hour postprandial glucose, if feasible
  - quarterly HbA_{1c}
  - yearly chemistry panel, fasting lipid profile, urinalysis (including microscopy and urine microalbumin screening)
  - thyroid stimulating hormone for type 1 and for type 2, as indicated
  - ECG in adults at baseline, and then as clinically indicated.

- Treatment plan, formulated after discussion with the multidisciplinary diabetes team and the patient, including measures to:
  - control blood glucose
  - control and treat diabetic complications
  - address and treat associated risk factors such as obesity, physical inactivity, smoking, hypertension, and dyslipidaemia.

- Referral, if feasible, to:
  - diabetes educator, to evaluate patient's ability to perform self-monitoring of blood glucose and his/her ability to interpret the data
  - dietician
  - foot-care specialist
  - ophthalmologist for annual retinal screening, or more often as indicated
  - nephrologists, neurologist, and cardiologist, if needed.

Chapter 6

Treatment options

Background

The backbone of diabetes management is proper diet and regular exercise, which have to be individualized [30,31]. Both could be the only management needed for controlling blood glucose in gestational diabetes, IGT and in type 2 diabetes in its early phase. Patients with type 2 diabetes may require oral hypoglycaemic agents and/or insulin, while type 1 patients need insulin therapy to survive.

The treatment plan for diabetes may include [23,25,31]:

- diabetes education
- meal planning and nutritional recommendations
- exercise
- anti-diabetic agents
- insulin
- management of associated conditions and complications.

The care of an individual with diabetes mellitus requires a multidisciplinary team. Central to success of this team are the patient's participation, input, and enthusiasm. Members of the health team include primary care provider and/or diabetologist, nutritionist, and a diabetes educator. When the complications of diabetes mellitus arise, sub-specialists including neurologists, podiatrists, nephrologists, vascular surgeon, cardiologists and ophthalmologists are essential. Comprehensive diabetes care, therefore, means that optimal diabetes therapy involves more than plasma glucose management. It should also detect and manage diabetes mellitus complications and modify diabetes mellitus-related risk factors [30].

Nutritional recommendations [23,31]

The goals of medical nutrition therapy that apply to all persons with diabetes mellitus are as follows.

- To attain and maintain optimal metabolic outcomes, including:
  - blood glucose levels in the normal range;
  - a lipid and lipoprotein profile that reduces the risk for macrovascular disease;
  - blood pressure levels that reduce the risk for vascular disease.

- To prevent and treat the chronic complications of diabetes; i.e. modify nutrient intake and lifestyle as appropriate for prevention and treatment of obesity, dyslipidaemia, cardiovascular disease, hypertension, and nephropathy.
- To improve health through healthy food choices and physical activity.
- To address individual nutritional needs, taking into consideration personal and cultural preferences and lifestyle while respecting the individual's wishes and willingness to change.

Diet composition for subjects with diabetes

Carbohydrates [23,30]

With regard to carbohydrates, there is strong evidence that the total amount of carbohydrate in meals or snacks is more important than the source or type. Hence sucrose and sucrose-containing foods do not need to be restricted by people with diabetes mellitus. It is important to note, however, that sucrose must be substituted for other carbohydrates gram for gram and not simply added to the meal plan. Non-nutritive sweeteners are safe for people with diabetes when consumed within the acceptable daily intake levels established by the FDA.

There is strong evidence that large amounts of dietary fibre (50 g/day) may have beneficial effects on glycaemia, insulinaemia, and lipaemia.

Proteins

During moderate hyperglycaemia, obese subjects with type 2 diabetes mellitus have an increased turnover of proteins compared to non-diabetic obese subjects. Based on this evidence, the protein requirements for diabetics may be greater than the recommended daily amount, but not greater than the usual intakes of 10%–20% of the total daily energy requirement. Limited evidence suggests that it may be prudent to avoid protein intake >20% of total daily energy, so as not to advance the development of diabetic nephropathy.

Fat

The primary goal regarding dietary fat in patients with diabetes is to decrease intake of saturated fat and cholesterol. Saturated fat is the principal dietary determinant of low-density lipid (LDL) cholesterol. Compared to non-diabetic subjects, diabetic subjects have an increased risk of coronary heart disease with higher intakes of dietary cholesterol.

Low-saturated fat (<10% of energy intake) and high-carbohydrate diets increase postprandial levels of plasma glucose and insulin, increase plasma triglycerides, and in some studies were shown to decrease plasma HDL cholesterol when compared to

isocaloric high mono-unsaturated fat diets. Therefore, if saturated fat calories need to be replaced, they can be replaced with carbohydrate or mono-unsaturated fat, either of which can contribute to a reduction in plasma LDL cholesterol.

There is strong evidence for the following statements.

- When compared with saturated fatty acids, poly-unsaturated fatty acids decrease plasma total and LDL cholesterol.
- When compared to poly-unsaturated fatty acid, mono-unsaturated fatty acids decrease plasma total and LDL cholesterol.
- Trans-fatty acids raise plasma LDL cholesterol and lower plasma HDL cholesterol; therefore their intake should be minimized.

General dietary recommendations for subjects with diabetes

For subjects with diabetes and a dyslipidaemic profile, the following distribution of nutrients is recommended [23,25] (Box 2).

If the diabetic subject has a normal lipid profile, then the carbohydrate intake can be increased to 55% of daily intake and the fat intake decreased to 25%–30%. Many individuals with type 2 diabetes mellitus are overweight (body mass index ≥25 kg/m^2), and approximately 36% are obese (body mass index ≥30 kg/m^2). As body adiposity increases, so does insulin resistance. Obesity may also aggravate dyslipidaemia and hypertension in patients with type 2 diabetes mellitus. Because of the effects of obesity on insulin resistance, weight loss is an important therapeutic objective for obese individuals with type 2 diabetes [23,25].

Box 2. Recommended distribution of nutrients for diabetic subjects

Carbohydrates	45%
Total fat	35%
Mono-unsaturated fatty acids	20%
Poly-unsaturated fatty acids	<8%
Saturated and trans-fatty acids	<7%
Protein	15%–20%
Cholesterol	<200 mg/day

Conclusion

Medical nutrition therapy for people with diabetes should be individualized, with consideration given to each individual's usual food and eating habits, metabolic profile, treatment goals, and desired outcomes. Ongoing nutrition self-management education and care need to be available for individuals with diabetes. In light of the existence of complexities of nutrition issues in diabetes, a qualified dietician knowledgeable and skilled in such issues is needed.

Exercise [30–35]

Exercise is extremely important in the management of diabetes because of its effect on blood glucose and free fatty acids. Exercise burns calories and helps to control weight, eases stress and tension, and maintains a feeling of well-being. In addition, regular exercise improves the body's response to insulin and may make oral anti-diabetic drugs and insulin more effective. It also promotes circulation, and lowers cholesterol and triglyceride levels, thus reducing the risk of cardiovascular disease.

Persons with diabetes should be encouraged to lead a normal life and participate in sports and exercise programmes. Generally they should not be excluded from physical activities or games, unless there are complications and on the advice of a physician. The main risk when exercising is hypoglycaemia, therefore blood glucose should be checked before exertion, and if appropriate, medication dosage may need to be reduced before exercise, or the individual may need to take an extra carbohydrate snack. Before starting any exercise programme, the health provider should do a thorough physical examination to find out whether or not it is safe for the patient to exercise.

Pharmacological therapy

When lifestyle modification fails, therapeutic methods should be used that consist of the following options:

- insulin sensitizers
- insulin secretagogues
- α-glucosidase inhibitors
- insulin.

Oral agents may counteract insulin resistance, improve ß-cell glucose sensing and insulin secretion, or control the rate of intestinal glucose absorption. Combinations of oral agents, in particular sulfonylureas plus metformin or thiazolidinediones plus metformin, have improved the care of diabetic patients, and may be used when monotherapy is ineffective [30]. Tables 15 and 16 show the different groups and their doses. Ultimately, the physician's judgment will direct the method of treatment.

Table 15. Types and mechanisms of action of oral anti-diabetic agents

Group	Name	Recommended daily dose	Mode of action
Insulin secretagogues			
Sulfonylureas	glibenclamide	5–20 mg/day	Stimulate insulin secretion
	glyburide	2.5–20 mg/day	Stimulate insulin secretion
	glipizide	2.5–20 mg/day	Stimulate insulin secretion
	glimepiride	1–8 mg/day	Stimulate insulin secretion
	gliclazide	40–160 mg/day	Stimulate insulin secretion
	gliclazide LA	30 mg/day	Stimulate insulin secretion
Benzoic acid derivative	repaglinide	3–16 mg/day	Stimulate insulin secretion
Phenylalanine derivative	nateglinide	180–360 mg/day	Stimulate insulin secretion
Insulin sensitizers			
Biguanide	metformin	0.5–2 gm/day	Decrease hepatic glucose production Increase insulin sensitivity
Thiazolidinediones	rosiglitazone	2–8 mg/day	Increase insulin sensitivity Decrease hepatic glucose production
	pioglitazone	15–45 mg/day	Increase insulin sensitivity Decrease hepatic glucose production
α-glucosidase inhibitors	acarbose	100–300 mg/day	Delays carbohydrate absorption
	miglitol	100–300 mg/day	Delays carbohydrate absorption

Table 16. Types and modes of action of insulin

Insulin		Onset of action	Peak action	Duration of action
Insulin alone				
Short-acting	regular/semilente	15–30 minutes	1–3 hours	5–7 hours
Intermediate-acting	NPH/lente	2–4 hours	8–10 hours	18–24 hours
Long-acting	ultralente	4–5 hours	8–14 hours	25–36 hours
Mixed insulin	regular/NPH (%)			
	30/70			
	50/50			
	20/80	1–2 hours	2–12 hours	6–24 hours
Insulin analogs				
Fast-acting	lispro			
	aspart	5–15 min	1–1.5 hours	3–4 hours
Long-acting	glargine	1–2 hours	no peak	24 hours

NPH: neutral protamine Hagedorn

Multidisciplinary mini clinics [23]

The use of multidisciplinary mini clinics for diabetes care has the potential to improve clinical outcome. These provide team care by a physician, nurse, dietician, chiropodist and health educator that will improve treatment and help establish a referral system for diabetic complications. Benefits of such an approach include:

- easy-to-apply standard guidelines within the clinic;
- better interaction and confidence among health care workers;
- improvement in the primary care physician's clinical skills;
- comprehensive management for the diabetic patient;
- fewer referrals to specialists and hospitals;
- early detection of high-risk patients, which is more cost-effective;
- structured preventive activities that are acceptable to the community;
- easy access for patients, which enhances compliance;
- better continuity of care.

The necessary tasks that should be performed by physicians (general practitioner, family medicine specialist, public health physician, primary health care physician, etc.) at the multidisciplinary mini clinic are as follows.

- assessing the medical condition of the patient and maintaining an appropriate medical record;
- providing appropriate management and therapy;
- assessing and detecting early complications;
- referring the patient to secondary and tertiary care as appropriate, and maintaining a system of follow-up;
- coordinating continuous medical and nursing education.

Chapter 7

Management recommendations for special groups and circumstances

Ramadan fasting [36]

Fasting is not recommended for type 1 diabetes because of the known increased risk of hypoglycaemia in this disorder, especially when patients are well controlled. Any decision by the patient to fast should be done after ample consultation and discussion with his/her physician. An individually-based insulin regimen using a basal-bolus method (such as glargine for basal insulin and pre-meal lispro) is a consideration for patients who insist on fasting. Close follow-up and frequent monitoring are essential.

It is not recommended for poorly-controlled type 2 patients to fast, because of the risk of dehydration associated with hyperglycaemia. Patients controlled by diet alone can fast. Patients treated with oral agents may fast if allowed by their physician, however their regimen will need to be adjusted. Metformin and thiazolidinediones are the preferred drugs, because they are associated with a lower risk of hypoglycaemia compared to insulin secretagogues. Short-acting insulin secretagogues are preferable to sulfonylureas. Insulin-treated patients may be treated like type 1 patients, using a basal-bolus method, or other regimens as recommended by the patient's physician. Close follow-up and frequent monitoring are essential.

Attention should be paid to the fast-breaking meal, particularly excessive intake of sweets and sweetened drinks, since this can lead to uncontrolled postprandial hyperglycaemia.

Hypertension

For the management of hypertension in patients with diabetes mellitus, the following approaches are recommended [23–25,27,37].

- Blood pressure should be checked at each patient visit.
- The target blood pressure level in all diabetes patients should be <130/80 mmHg.
- Lifestyle modification (exercise, healthy diet, reducing weight and sodium intake) can lower blood pressure.

- Thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and ß-blockers are good initial therapy options in the treatment of uncomplicated hypertension.
- Calcium channel blockers and α-blockers can be used, but as second-line therapy.
- In patients with microalbuminuria, ACE inhibitors or ARBs are the drugs of choice.
- In patients with congestive heart failure, ACE inhibitors are preferred.
- ß-blockers are especially useful post-myocardial infarction.
- In patients with macroalbuminuria, careful follow-up of serum creatinine and potassium is recommended if diuretics, ACE inhibitors or ARBs are used.
- Combination drug therapy is needed in a large number of patients in order to achieve target blood pressure.
- In the elderly, blood pressure should be lowered in a gradual fashion and over a longer period of time in order to avoid complications related to organ hypoperfusion.

Figure 3 is a suggested protocol for management of hypertension.

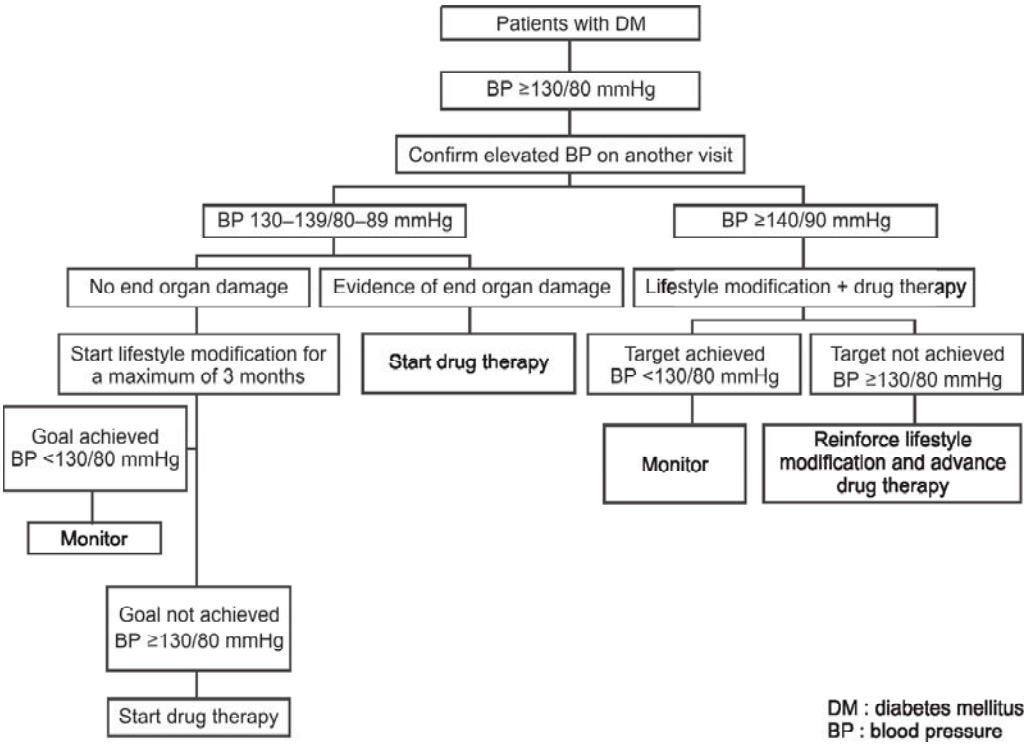


Figure 3. Suggested protocol for the management of hypertension

Dyslipidaemia

Management goals of diabetic dyslipidaemia

The primary target of therapy is LDL cholesterol, unless serum triglycerides are ≥500 mg/dL in which case triglyceride-lowering therapy should be started immediately because of the high risk of pancreatitis. If or when triglycerides levels are <500 mg/dL, the primary target of treatment is LDL cholesterol and the goal LDL for patients with coronary heart disease or coronary heart disease-equivalent, including diabetes, is an LDL cholesterol <100 mg/dL. When this is achieved, attention can then be focused on triglycerides. If triglycerides are ≥200 mg/dL, the sum of LDL plus very low density lipid (VLDL) cholesterol (also referred to as non-HDL cholesterol) becomes the secondary target, since VLDL, and especially its remnants, are considered atherogenic.

For patients with low HDL cholesterol (<40 mg/dL), interventions to raise HDL cholesterol level may be considered but only after the goals for LDL cholesterol and non-HDL cholesterol (for patients with triglycerides ≥200 mg/dL) have been achieved.

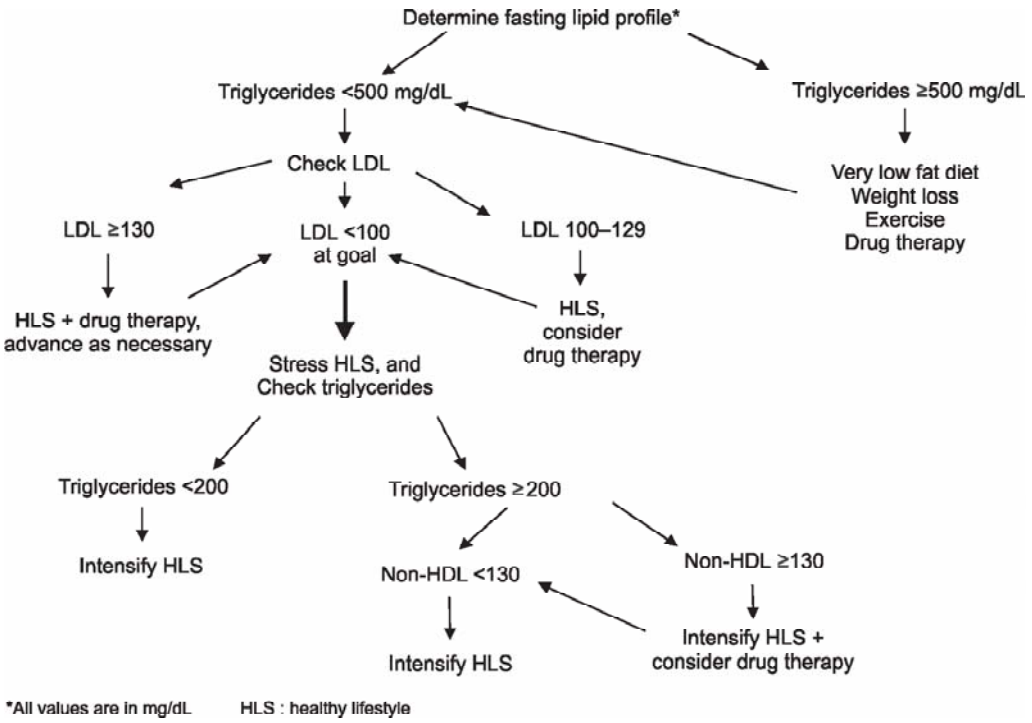


Figure 4. Management of dyslipidaemia

There is no goal specified for raising HDL in patients with isolated low HDL cholesterol. However, even minimal elevation of HDL should translate into improvement in cardiovascular risk. It is recommended to start statin therapy in patients with LDL cholesterol ≥100 mg/dL if they have a history of coronary heart disease.

Lipid profiles should be repeated for confirmation when in doubt. Figure 4 summarizes the protocol for managing dyslipidaemia.

Healthy lifestyle changes

Dietary interventions, the cornerstone of diabetes management, are also an important means of controlling dyslipidaemia in both diabetic and non-diabetic individuals. Considerable evidence demonstrates the beneficial changes in diabetic dyslipidaemia following dietary alterations such as changes in nutrient composition.

Exercise is as an important method of improving diabetes control and reducing the risk of cardiovascular disease; additional evidence suggests that it has beneficial effects on dyslipidaemia, such as significantly increasing HDL cholesterol levels.

Healthy lifestyle practices should therefore be emphasized in patients with diabetes. They include:

- increased physical activity
- weight reduction for obese patients
- reduction of food items high in cholesterol, saturated fats and trans-fatty acids
- increased intake of viscous (soluble) fibres and of plant stanols and sterols which help lower serum cholesterol by limiting its absorption from the gut.

In patients with elevated triglycerides and low HDL, increasing the intake of unsaturated fat and decreasing carbohydrates may help correct the lipid abnormalities. A model for lipid management is shown in Figure 5.

Drug therapy for diabetic dyslipidaemia

Most patients with diabetes and dyslipidaemia will require drug therapy in order to reach their goals. Different classes of medications are available, with variable effects on LDL, HDL and triglycerides. The following section outlines the characteristics of the commonly used drug classes.

HMG CoA reductase inhibitors

Hydroxymethylglutaryl coenzyme A reductase inhibitors (HMG CoA), or statins, are currently considered the drugs of choice for treatment of high LDL cholesterol. Some statins, especially the more potent ones, can also lead to significant lowering of

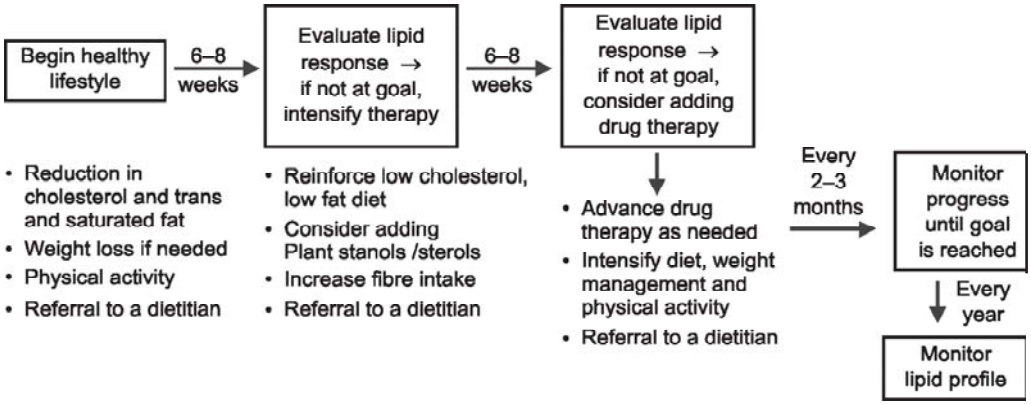


Figure 5. Protocol for lipid management

triglycerides. Statins reduce LDL cholesterol by 18%–55% and reduce triglycerides by 7%–30%. They raise HDL cholesterol by 5%–15%.

- Major side effects:
  - myopathy or rhabdomyolysis (rare)
  - increase in liver enzymes (usually reversible).
- Contraindications:
  - absolute: liver disease
  - relative: use with certain drugs, due to potential for interaction and increased risk of myopathy.
- Demonstrated therapeutic benefits:
  - reduce major coronary events
  - reduce coronary heart disease mortality
  - reduce coronary procedures (bypass surgery, percutaneous transluminal coronary angioplasty)
  - reduce stroke
  - reduce total mortality.

Statin	Dose range
lovastatin	20–80 mg
pravastatin	20–40 mg
simvastatin	20–80 mg
fluvastatin	20–80 mg
atorvastatin	10–80 mg
rosuvastatin	5–40 mg

Bile acid sequestrants

Bile acid sequestrants are considered second-line therapy for high LDL cholesterol, usually taken in combination with statins. They can be used as first-line therapy in patients who are allergic or intolerant of statins.

- Major actions:
  - reduce LDL cholesterol by 15%–30%
  - raise HDL cholesterol by 3%–5%
  - may increase triglycerides.
- Side-effects:
  - gastrointestinal distress/constipation
  - decreased absorption of other drugs when taken concomitantly.
- Contraindications:
  - dysbetalipoproteinemia
  - raised triglycerides (especially >400 mg/dL).
- Demonstrated therapeutic benefits:
  - reduce major coronary events
  - reduce coronary heart disease mortality.

Drug	Dose range
cholestyramine	4–16 g
colestipol	5–20 g
colesevelam	2.6–3.8 g

Cholesterol absorption inhibitor

Cholesterol absorption inhibitor is a new class of cholesterol-lowering medication, aimed at lowering LDL cholesterol. The compound in this class is typically used in combination with a statin when further LDL lowering is desired.

- Major actions:
  - reduce LDL cholesterol by 15%–20%
  - raise HDL cholesterol by 3%–4%
  - no effect on triglycerides.
- Side-effects:
  - minimal.

Drug	Dose
ezetimibe	10 mg

Nicotinic acid

Despite its side-effects, nicotinic acid may be a useful agent in managing diabetic dyslipidaemia. It can lead to significant improvement in triglyceride and HDL cholesterol levels, the two most common abnormalities in patients with diabetes. Nicotinic acid may lead to a mild increase in blood glucose, however this hyperglycaemic effect may be reduced if the drug dosage is kept below 2 g/day. A mild increase in HbA_{1c} is to be expected at dosages of over 1500 mg. Such an increase may be remedied by adjusting diabetes therapy.

- Major actions:
  - lowers LDL cholesterol by 5%–25%
  - lowers triglycerides by 20%–50%
  - raises HDL cholesterol by 15%–35%.
- Side-effects:
  - flushing
  - hyperglycaemia
  - hyperuricaemia
  - upper gastrointestinal distress
  - hepatotoxicity.
- Contraindications
  - liver disease
  - severe gout
  - peptic ulcer disease.
- Demonstrated therapeutic benefits:
  - reduces major coronary events
  - possible reduction in total mortality.

Drug form	Dose range
immediate release (crystalline)	1.5–3 g
extended release	1–2 g

Fibric acids

Fibrates are considered first-line therapy for patients with high triglycerides (and adequate LDL). The newest agent, fenofibrate, appears to have a lower potential for drug–drug interaction.

- Major actions:
  - lower LDL cholesterol by 5%–20% (with normal triglycerides)
  - may raise LDL cholesterol (with high triglycerides)

  - lower triglycerides by 20%–50%
  - raise HDL cholesterol by 10%–20%.
- Side-effects:
  - dyspepsia
  - gallstones
  - myopathy (especially in patients with renal impairment).
- Contraindications:
  - significant renal or hepatic disease.
- Demonstrated therapeutic benefits:
  - reduce progression of coronary lesions
  - reduce major coronary events.

Drug	Dose
clofibrate	1000 mg, twice daily
gemfibrozil	600 mg, twice daily
fenofibrate	160 mg, once daily

Omega-3 fatty acids (fish oils)

The major role of fish oil is in management of high triglycerides, usually as second- or third-line therapy.

Form	Dose
fish oil	1–3 g daily

Combination therapy

A large number of patients with diabetes and dyslipidaemia will require combination therapy in order to achieve their goals. Such a situation may occur because one drug is not enough to reach a desirable level for a particular lipoprotein, or because they have a combination of elevated LDL cholesterol and elevated triglycerides, thus requiring dual therapy. Table 17 shows commonly used combinations of lipid-lowering agents.

Table 17. Commonly used combinations of lipid-lowering agents

Combination	Used for	Risk
Statin + bile acid-binding resin	High LDL	Resin may raise triglycerides
Statin + ezetimibe	High LDL	No increased risk
Statin + fibrate	High LDL + high TG	Risk of myositis
Statin + nicotinic acid	High LDL + high TG	
	or	
	High LDL + low HDL	Risk of myositis
Fibrate + nicotinic acid	High TG	
	or	
	High TG + low HDL	Risk of myositis (low)

TG: triglycerides

Glycaemic control and dyslipidaemia

Improvement in glycaemic control can lead to a less atherogenic lipid profile. Elevated triglycerides tend to improve consistently when glucose levels are lowered, however the effect of better glucose values tends to be more variable with regard to HDL cholesterol and LDL cholesterol levels.

Insulin has a consistent effect in lowering triglycerides in poorly controlled patients, while its effects on other lipids tend to be variable. In addition, better glycaemic control is likely to reduce the amount of glycated LDL, and therefore reduce LDL atherogenicity.

Always look for secondary causes of dyslipidaemia and treat accordingly. Reinforcing a healthy lifestyle (adequate diet, weight loss, exercise) is recommended as a first step for management of dyslipidaemia.

Aspirin therapy

Aspirin therapy (75–162 mg/day) is indicated as a secondary prevention in diabetic patients with evidence of cardiovascular disease. It is also indicated as primary prevention for cardiovascular disease in patients at risk, such as those aged above 40 years, with hypertension, a smoking habit, obesity, dyslipidaemia. Contraindications to aspirin use include:

- patients with bleeding tendency or at risk of bleeding
- allergy
- active hepatic disease
- recent gastro-intestinal bleeding
- those aged <30 years because of the risk of Reye syndrome (a hepatic disease that was associated with aspirin therapy in children) [23].

Chapter 8

Acute complications of diabetes mellitus

Hypoglycaemia

Definition

Hypoglycaemia in patients with diabetes mellitus is an abnormally low concentration of glucose in the blood caused by insufficient food intake, excessive exercise, or overdosage with oral hypoglycaemic agents or insulin.

Background

The development of hypoglycaemia is an ever-present possibility in all patients with diabetes treated with insulin or oral hypoglycaemic medications. A person with hypoglycaemia may feel nervous, shaky, weak, or sweaty. They may have a headache, blurred vision, and be very hungry. In more serious instances, they may become unconscious [21]. Taking small amounts of sugar or glucose-containing juice or food will usually help the person feel better within 10–15 minutes.

The serious consequences of hypoglycaemia relate to its effects on the brain, including loss of cognitive function, seizure and coma. Prolonged or repeated episodes of hypoglycaemia may produce permanent brain damage, and the adrenergic response to the condition may be dangerous in people with cardiovascular disease.

The risk of hypoglycaemia is particularly high when tight glycaemic control is sought. In the Diabetes Control and Complications Trial [29] there was a three-fold increase in the risk of severe hypoglycaemia, including coma and/or seizures, when intensive insulin therapy was used. These episodes may occur with disproportionate frequency at night. Patients with autonomic neuropathy may have greater difficulty in detecting symptoms of hypoglycaemia and/or recovering from it. ß-adrenoreceptor blockers may also impair detection of symptoms and/or recovery, and alcohol consumption may aggravate the risk of hypoglycaemia and impair recovery. Delayed or missed meals and increased physical activity increase the risk of hypoglycaemia. Oral hypoglycaemic agents, particularly sulfonylureas, may also induce hypoglycaemia.

Although good glycaemic control is the target in most diabetic individuals; there are some situations where strict control is not recommended because of the increased risk of hypoglycaemia. Higher blood glucose targets should be selected for those patients. They may include patients:

- who are very young (aged below 7 years) or very old;
- with decreased life expectancy because of terminal illness (i.e. cancer);
- with hypoglycaemia unawareness;
- with advanced retinopathy before control by photocoagulation;
- with unstable angina pectoris or transient cerebral ischaemic attacks;
- with history of generalized seizures;
- who do not spontaneously recover from hypoglycaemia (counter-regulatory unresponsiveness).

Hypoglycaemia as a result of physical activity

For sporadic physical activity departing from the patient's usual daily routine, action needs to be taken to avert hypoglycaemia. Such action might include consumption of extra carbohydrate food to cover the increased activity. Initially, this may be 10–15 g of carbohydrate every 30–45 minutes during increased activity. Blood glucose should be monitored before, during and after exercise to determine the effectiveness of this intervention.

Another option is to reduce the dose of insulin either in addition to, or instead of, giving dietary carbohydrate supplements. All patients should have quick-acting, rapidly-absorbed carbohydrate available when exercising in case of hypoglycaemia. Patients should realize that moderately intensive exercise may deplete glycogen stores, resulting in a sustained food requirement to replace the glycogen. As a consequence, hypoglycaemia may occur well after exercise (e.g. 12 hours after jogging). For this reason, patients should be cautious when planning vigorous physical activity in the evening hours.

Prevention strategies

- Education of patients and their families about the prevention, recognition and treatment of hypoglycaemia is essential and is, therefore, the most important approach.
- Health care workers, particularly emergency medical personnel, should be familiar with the recognition and treatment of hypoglycaemia.
- To facilitate prompt assessment, patients receiving insulin treatment should wear or carry appropriate identification.
- Blood glucose targets must be individualized for each patient.

- Patients who no longer experience the usual warning symptoms should be carefully instructed in subtle clues to hypoglycaemia (e.g. minor changes in mental function, perioral paraesthesia) besides having their glycaemic targets raised.
- There should be a careful balance of food intake, activity and insulin dosage in both quantity and timing, taking into consideration the eating and other lifestyle habits of the individual
- Meals should be consumed on time, and appropriate changes made in insulin dosage if meals have been omitted.
- Between-meal and bedtime snacks may be necessary to reduce the risk of hypoglycaemia.
- Energy intake should meet the needs of usual daily activity.
- Patients should carry rapidly absorbable carbohydrate with them at all times.
- It may be desirable to measure blood glucose before driving a motor vehicle or operating potentially dangerous equipment, both at leisure and in the workplace.

When economically feasible, glucagon should be available in the home (and possibly in the school, day-care centre or workplace) of insulin-treated patients, especially those at particular risk of hypoglycaemia. Family members, teachers and colleagues should be instructed in the proper use of glucagon in an emergency. Glucagon should be available in emergency rooms, in emergency vehicles and in first-aid kits in all aircraft used in commercial aviation and personnel should be familiar with its use.

When hypoglycaemia arises in patients treated with sulfonylureas, it should be recognized that these agents persist in the circulation for a long time, and that hypoglycaemia may recur after its initial correction. Such patients should be monitored for an appropriate period after therapy is changed, depending on the sulfonylurea originally used.

Any changes in insulin preparation, formulation, concentration or species should be accompanied by appropriate education of individuals with diabetes, health professionals and all other people involved in diabetes health care.

Hyperglycaemic crisis

Diabetic ketoacidosis and the hyperglycaemic hyperosmolar state [21–23]

Ketoacidosis mainly affects people with type 1 diabetes. Diabetic ketoacidosis remains a potentially lethal condition with mortality as high as 10%–15%; however, at least 50% of cases are avoidable. Many new patients with type 1 diabetes mellitus present with ketoacidosis, so early recognition and diagnosis are clearly of importance.

Ketoacidosis occurs when the body breaks down fatty acids and produces ketones, which are acidic. Some of the ketone bodies are lost through the urine, but those that remain will build up in the blood and lead to ketoacidosis. Signs of ketoacidosis include:

- nausea
- vomiting
- dry skin and mouth
- deep, rapid breathing
- low blood pressure.

If the person is not given fluids and insulin right away, ketoacidosis can lead to death.

It is crucial to educate patients and health care personnel about precipitating factors and actions to be taken to avoid ketoacidosis. Major precipitating factors include infection and other acute illnesses. In such situations, insulin requirements are likely to increase. Omission or insufficient insulin intake is a major cause of diabetic ketoacidosis in some parts of the world. With proper instruction on monitoring of blood glucose and urine ketones, insulin dose adjustment and maintenance of fluid intake, many potential cases of diabetic ketoacidosis can be prevented. If vomiting occurs, early referral for intravenous therapy is required.

It is rare for people with type 2 diabetes mellitus to develop ketoacidosis. It is much more common for them to develop the hyperglycaemic hyperosmolar state in the face of severe infection or other major intercurrent illness. They usually present with dehydration, circulatory compromise and a change in mental state. Acidosis is uncommon, except when related to lactic acidosis due to hypoperfusion.

Serum ketones and electrolytes need to be monitored. Bicarbonate administration for type 1 diabetes is not recommended except in severe acidosis (pH <7.1). Potassium level needs to be checked every 2 hours and corrected as needed. Other electrolytes that need follow-up are phosphorus and magnesium. A suggested protocol for the management of hyperglycaemic crisis in adults is shown in Figure 6.

Infections

People with poorly controlled diabetes are more prone to develop bacterial (in particular anaerobic), mycobacterial and fungal infections. Diabetics are more prone to urinary tract infections after bladder instrumentation than non-diabetic individuals. Urinary tract infections may also result from obstruction or neurogenic bladder. Pyelitis and pyelonephritis aggravate diabetic nephropathy. Chronic painless infection may destroy a neuropathic and/or ischaemic foot.

Tuberculosis of respiratory and other organ systems, fungal infections of skin, bacterial infections of the urinary tract and anaerobic infections of deep tissues pose serious health threats, particularly in poor hygienic surroundings. Not only do they precipitate diabetic ketoacidosis but, if not treated promptly and effectively, advancing infections may directly threaten survival.

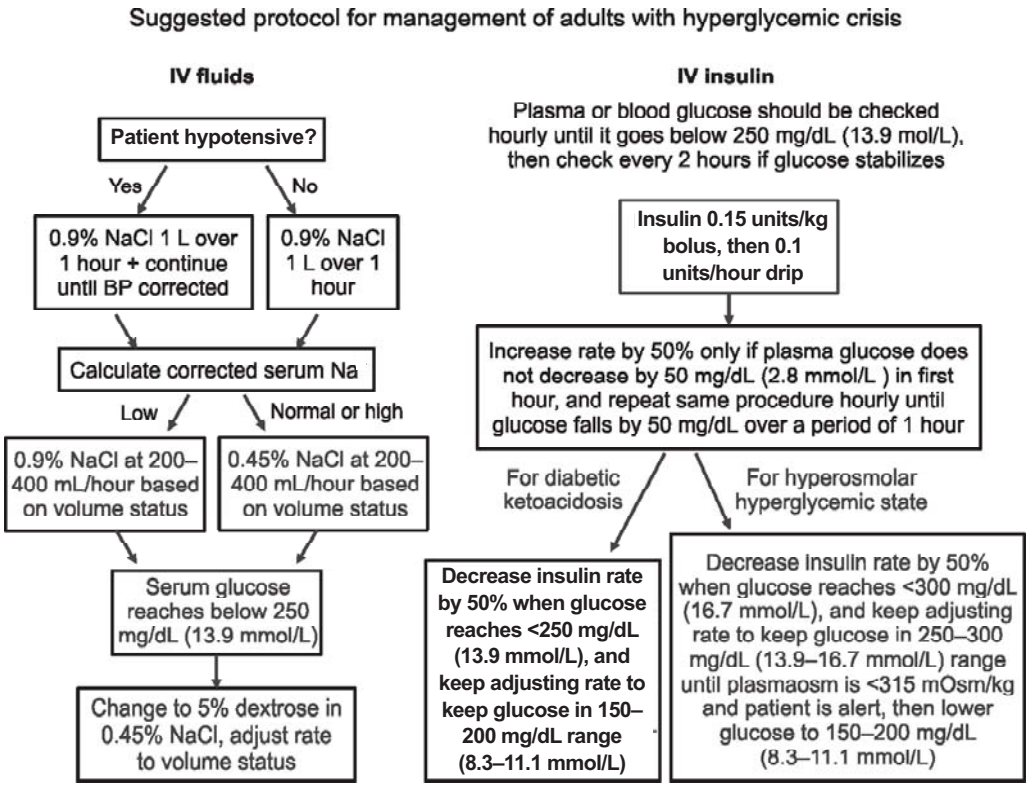


Figure 6. Suggested protocol for management of adults with hyperglycaemic crisis

Chapter 9

Chronic complications of diabetes

Atherosclerosis

Atherosclerosis is the most common macrovascular complication of diabetes mellitus [38,39]. It accounts for 75% of diabetes-related deaths, a figure two to three times higher than that in people without diabetes. In the Eastern Mediterranean Region, some studies have reported that the occurrence of clinical events related to coronary artery disease are four times higher in patients with diabetes [13,40]. Coronary and cerebrovascular diseases are also two to three times more common, and post-infarction mortality higher. These increases in atherosclerosis in diabetic individuals are seen in all populations, whether the general incidence of atherosclerosis is high or low. In developing and rural societies, changes in lifestyle to a pattern similar to that of more industrialized and urban societies are often associated with a general increase in atherosclerosis.

Although the largest numbers of diabetic ischaemic events occur in people with type 2 diabetes mellitus, the risk of atherosclerosis is also high in type 1 and may be manifest at a young age. One feature unique to women with diabetes is the loss of protection from atherosclerosis prior to menopause.

Hyperglycaemia may promote atherosclerosis by:

- modifications of lipoproteins (e.g. glycation of LDL)
- glycation of arterial wall proteins
- formation of advanced glycation end-products
- stimulation of insulin secretion
- stimulation of protein kinase C.

Hyperinsulinaemia has been shown to be independently associated with coronary disease in men. It has also been shown in cross-sectional studies to be associated with coronary disease in both men and women. Whether hyperinsulinaemia plays a role in the development of atherosclerosis, or represents a mere non-causal association, remains to be clarified.

Obesity, particularly abdominal obesity, is another factor closely linked to atherosclerosis and diabetes. Its impact may be mediated, at least in part, through increased insulin resistance and hyperinsulinaemia, dyslipoproteinaemia and hypertension, or a combination of these factors.

Many factors that predispose non-diabetic individuals to atherosclerosis are also associated with atherosclerosis in people with diabetes. These factors include smoking, hypertension and hypercholesterolaemia. There is a vast body of evidence to show that smoking greatly increases atherosclerosis, particularly in those with diabetes. There is also a great increase in the risk of macrovascular disease in people with urinary albumin excretion exceeding 30 mg/24 hours and in those with clinical nephropathy. People with these characteristics are therefore important targets for prevention.

People with diabetes should therefore be screened for risk factors for macrovascular disease (cardiovascular, cerebrovascular and peripheral vascular). There is ample evidence that aspirin intake confers both primary and secondary prevention against cardiovascular disease in patients with diabetes. Its use is highly recommended.

Retinopathy

Background

Diabetic retinopathy is the leading cause of blindness and visual impairment in adults in many societies. Almost everyone with younger-onset type 1 diabetes will develop diabetic retinopathy after 20 years of the disease. At some time during their lives, 75% will develop the most severe stage, proliferative diabetic retinopathy. In older-onset type 2 diabetes mellitus, almost 60% will develop diabetic retinopathy and at some time during their lives about 10% will develop proliferative retinopathy and about 2% become blind.

Both younger- and older-onset diabetic people are at risk of developing another sight-threatening manifestation of diabetic retinopathy, namely macular oedema, a swelling of the central part of the retina. Epidemiological data also suggest that loss of vision due to open-angle glaucoma and cataract may be more common in people with diabetes than in non-diabetics [21].

Women with known diabetes mellitus who are planning a pregnancy should have a detailed examination and should be counselled about the potential risk of development and/or rapid progression of retinopathy during pregnancy.

There are two main factors that delay the discovery of diabetes eye complications.

- Physician factors:
  - failure to dilate pupils on examination;
  - poor ophthalmoscopy skills;
  - lack of knowledge of the benefits of photocoagulation.

- Patient factors:
  - lack of awareness of the presence of vision-threatening retinopathy because it is often asymptomatic;
  - lack of knowledge of, access to and availability of care.

Screening strategies

A number of screening strategies have been recommended for the detection of diabetic retinopathy. Patients with type 1 diabetes mellitus should have an initial eye examination within the first 3–5 years after diagnosis, while patients with type 2 diabetes mellitus should be screened soon after diagnosis. Subsequent examinations should be done on a yearly basis.

Screening should be done by adequately trained personnel, such as an ophthalmologist with an interest in diabetic eye disease. When this is not feasible and the patient is not under the care of an ophthalmologist, it is recommended that screening be the primary responsibility of the primary care physician or organization. It should be done in close collaboration with the nearest ophthalmological facility that can further assess and treat diabetic retinopathy, glaucoma and cataract. Non-physician screeners should be properly trained and qualified.

An eye examination should include:

- a history of the onset of visual symptoms;
- any history of glaucoma and cataract;
- measurement of visual acuity unaided and, if necessary, with glasses and/or a pinhole to obtain an estimate of best-corrected visual acuity;
- pupil dilatation;
- lens examination for cataract with a +10 lens in the ophthalmoscope or red reflex photography;
- fundus examination by direct ophthalmoscopy (which is inexpensive and widely available, but not very sensitive);
- where feasible, proper screening should be performed by an ophthalmologist, using dilated indirect ophthalmoscopy coupled with biomicroscopy or 7-field stereoscopic retinal photography.

Fundus photography using a standard or non-mydriatic camera is more expensive than ophthalmoscopy, however its advantages include a more permanent objective record which can be produced by technical personnel. These images can be assessed at a later time by a specialist.

There should be established channels for rapid referral of patients with sight-threatening retinopathy. If screening is carried out by retinal photography, the pictures

should be taken by medical photographers and evaluated by experienced readers who should then report back to the organization responsible for the screening and to the patient. People with diabetes should he encouraged to report any significant changes in visual acuity not related to changes in blood glucose to their primary care providers or their eye doctors. Findings that indicate the need for immediate referral to an ophthalmologist for further management are:

- pre-proliferative retinopathy;
- venous irregularities (beading, reduplication, etc.), multiple retinal haemorrhages, multiple cotton-wool spots, or intraretinal microvascular abnormalities;
- non-proliferative retinopathy with macular involvement, leading to reduced visual acuity not corrected by pinhole, or haemorrhages;
- hard exudates within one disc diameter of the macula, with or without visual loss;
- non-proliferative retinopathy without macular involvement but with large circinate hard exudates material;
- proliferative retinopathy.

Emerging review by an opthalmologist should occur for:

- sudden loss of vision
- rubeosis iridis
- preretinal or vitreous haemorrhage
- retinal detachment

Rapid review by an opthalmologist should occur for new vessel formation.

Intervention strategies

There are no drugs available to prevent the development or progression of retinopathy in humans. Neither aspirin nor aldose reductase inhibitors have proved beneficial.

The medical benefits are now obvious for the efficacy of pan-retinal laser photocoagulation for eyes with advanced proliferative retinopathy, and local laser photocoagulation for eyes with clinically significant vision-threatening macular oedema. Clinical trials have demonstrated the benefit of laser photocoagulation for severe proliferative retinopathy and clinically significant macular oedema. Recent findings from one study suggest that timely treatment may prevent up to 90% of severe visual loss associated with proliferative retinopathy.

The United Kingdom Prospective Diabetes Study group [27,28] has shown that there is an association between blood pressure and the incidence and progression of retinopathy. Tight blood pressure control in people with hypertension with antihypertensive drugs will help prevent or delay retinopathy.

Potential obstacles to prevention include:

- lack of awareness by patients of sight-threatening retinopathy because it is often asymptomatic (an important reason why patients are not necessarily examined for retinopathy);
- lack of awareness by primary care physicians of the benefits of timely detection and treatment with photocoagulation;
- lack of the necessary ophthalmoscopy skills by primary care physicians;
- lack of laser equipment to treat retinopathy;
- lack of skilled ophthalmologists to treat retinopathy when lasers are available;
- lack of economic resources to seek and secure care.

Setting goals

The major goal is to reduce blindness. This can be achieved by:

- educating patients about the need for ophthalmologic care with examination of the retina through dilated pupils;
- educating primary care providers about the benefits of detection of retinopathy and referral of their patients for appropriate eye care;
- developing methods of achieving good glycaemic control in an attempt to prevent the development of retinopathy, and promoting good glycaemic control as a possible approach to the reduction of diabetic retinopathy once it occurs;
- ensuring that facilities (with laser technology) are available for photocoagulation treatment of retinopathy.

Evidence statements

- eye surveillance for adults newly diagnosed with type 1 diabetes should be started from diagnosis;
- structured eye surveillance should be at one year interval;
- digital photography best meets the needs of appropriate sensitivity/selectivity, feasibity and opportunities for quality assurance [27,41].

Conclusions

To prevent retinopathy and visual loss, the following are recommended:

- promotion of good glycaemic control;
- control of blood pressure;
- detection and treatment of cataract;
- detection and treatment of glaucoma at an early stage.

Diabetic nephropathy

Background

Diabetic nephropathy (kidney disease) is the most common cause of renal failure in many Eastern Mediterranean Region countries [42,43] and a major cause of premature death in diabetic patients. Diabetic patients are 17 times as prone to kidney disease as non-diabetic people. It is a multistage condition that requires several years to become clinically overt. The stages are as follows:

- incipient (sub-clinical) nephropathy
- clinical (or overt) nephropathy
- advanced nephropathy
- end-stage renal disease.

Incipient nephropathy is defined by a persistent increase in albumin excretion rate, referred to as microalbuminuria without frank proteinuria. It is represented by an albumin excretion rate of 20–200 µg/minute (30–300 mg/24 hours). Microalbuminuria may be accompanied by a rise in blood pressure. Clinical nephropathy is defined by the presence of persistent proteinuria, i.e. albumin secretion >200 µg/minute (>300 mg/24 hours), and is usually accompanied by hypertension. In advanced nephropathy there is a significant decline in glomerular filtration rate and the appearance of symptoms of uraemia and/or nephrotic syndrome. End-stage renal disease necessitates dialysis or renal transplantation.

While the cumulative risk of diabetic nephropathy in type 1 diabetes mellitus is about 30%–40% after 25–30 years, it varies considerably in type 2 diabetes mellitus depending on ethnic origin, and can be as low as 15% in some groups of European origin after 25 years of disease.

Screening strategies

Blood pressure should be monitored at least annually in all patients with diabetes mellitus, and preferably twice a year. All those who have had type 1 diabetes mellitus for over 5 years and are aged ≥12 years and all patients with type 2 diabetes mellitus should have their urinary albumin excretion measured at least once a year until the age of 70. It should be appreciated that albumin excretion rate is increased by:

- heavy exercise
- urinary tract infection
- acute illness
- high protein intake
- decompensation of metabolic control, including recent ketoacidosis
- cardiac failure.

An elevated albumin excretion rate should be confirmed by repeated testing. The urinary microalbumin test is a convenient method. It has been demonstrated that the onset of nephropathy in type 1 diabetes mellitus patients can be detected many years earlier using this method than by screening for proteinuria. Patients with an elevated albumin excretion rate should be monitored at least every 6 months and more often if required by clinical conditions and/or treatment strategies. Such monitoring should also include regular assessment of HbA_{1c}, blood pressure, serum creatinine and serum lipids. If overt nephropathy appears, creatinine clearance should be measured at least annually, and more frequently if indicated by clinical conditions.

Intervention strategies

Frequency, severity and progression of diabetic nephropathy are related to the degree of hyperglycaemia and the duration of diabetes mellitus. The progression and severity of kidney disease are also associated with any elevation of blood pressure, and are profoundly influenced by the effectiveness of the control of coexisting hypertension.

A number of factors may slow the progression of renal damage. These include:

- careful control of hyperglycaemia (since moderate hyperglycaemia results in increased renal perfusion);
- meticulous control of hypertension, with particular attention to antihypertensive strategies that prevent increases of intra-capillary pressure within the kidney, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.
- dietary protein restriction (since protein is also vasodilatory in the kidney and leads to increased renal perfusion).

In addition to glucose and blood pressure control, and limitation of protein intake, other measures may need to be taken including:

- appropriate treatment of associated lipid abnormalities;
- interventions based on clinical indications should be used to limit metabolic bone disease and anaemia;
- if fluid retention occurs, loop rather than thiazide diuretics should be given;
- symptomatic and supportive treatments are necessary to reduce the impact of diabetic nephropathy;
- as end-stage renal disease evolves, there should be early referral for consideration for renal replacement therapy (dialysis or transplantation).

In order to decrease renal damage from any cause, other precautions should be taken. Patients should be checked for urinary tract infections, which should be treated vigorously. Appropriate precautions should be taken before radiography, such as judicious hydration, as radiographic contrast media may provoke sudden and severe deterioration

in the damaged kidney. Potentially nephrotoxic drugs should be avoided, if possible, in patients with diabetes and particularly those with any stage of nephropathy.

Potential obstacles to prevention of nephropathy include:

- lack of awareness by primary care physicians about the benefits of careful glycaemic and blood pressure control in preventing renal disease and of timely detection and treatment, particularly of incipient nephropathy;
- lack of economic resources to provide care;
- lack of donated kidneys for transplantation;
- feelings of hopelessness on the part of patients and health-care providers.

Needs

There is a need:

- for continued collection of data to monitor the effectiveness of interventions;
- to educate patients and primary care physicians about the value of detection and the benefits of treatment of nephropathy;
- to achieve good glycaemic and blood pressure control in an attempt to minimize the development of nephropathy;
- to reduce the economic barriers preventing patients from seeking appropriate care when necessary.

Monitoring and evaluation

In the case of end-stage renal disease, national and regional databases are needed to provide information on:

- the identity of patients requiring renal replacement therapy;
- objective programmes for educating and testing the knowledge of primary care physicians;
- how to evaluate patients' knowledge about diabetic nephropathy and recommended care both before and after educational programmes;
- how to evaluate the success of programmes by monitoring changes in behaviour;
- how to evaluate the cost-effectiveness of programmes.

Evidence statements:

There is a general agreement on annual screening, and on the albumin:creatinine ratio as preferred method of detection, but cut-off values differ somewhat, microalbuminuria being defined as 30 mg in USA, 2.0/2.8 mg/mmol (men/women) in Canada and 2.5/3.5 mg/mmol in Europe. Monitoring of changes in glomerular filtration rate (GFR) is

emphasized in all guidelines, which recommend serum creatinine measurement, and more recently emphasize the need for calculation of estimated GFR.

Conclusions

Tighter blood pressure and glycaemic control is needed in patients at risk of developing diabetic nephropathy. Vigorous treatment of clinical nephropathy may delay the development of end-stage renal disease. One of the highest priorities at the present time is the education of patients and their physicians about the potential for early detection and prevention of diabetic kidney disease. The likelihood of success in preventing and reducing the consequences of diabetic kidney disease will depend on the availability of resources to implement educational programmes and to monitor them continuously [22,23].

Diabetic neuropathy

Background

Diabetic neuropathy is a nerve disorder that may be clinically evident or sub-clinical, and which occurs in diabetes mellitus in the absence of other evident etiology. Manifestations may occur in both the peripheral and the autonomic nervous systems [44].

Peripheral neuropathies include:

- polyneuropathies, e.g. distal sensory-motor neuropathy and proximal motor neuropathy;
- focal neuropathies, e.g. mono-neuropathies (including cranial) and entrapment neuropathies;
- multifocal neuropathies.

Autonomic neuropathies may involve the following systems:

- cardiovascular
- gastrointestinal
- genitourinary [22].

The most common form of neuropathy is distal symmetrical sensory–motor polyneuropathy, which can be divided into three stages: early, symptomatic and severe. Early distal sensory–motor neuropathy is usually asymptomatic, but sensory abnormalities may be detectable by neuro-physiological testing. Symptomatic distal sensory-motor neuropathy is manifested by sensory loss, and may be accompanied by paraesthesia and/or pain. Severe distal sensory–motor neuropathy is manifested by motor involvement, and may be accompanied by disabling symptoms and the potential for ulceration, which can lead to infection, necrosis, gangrene, and loss of the limb.

Diabetic neuropathy is possibly the most common microsvascular complication of diabetes mellitus.

Hyperglycaemia associated with diabetes is thought to be central to the effect on nerve structure through a number of possible mechanisms, including increased activity in the polyol pathway, altered myo-inositol metabolism and non-enzymatic glycation. Other mechanisms may also be involved, e.g. alterations in nerve growth factor activity, blood viscosity, circulating platelets and the rate of synthesis and transport of intra-axonal protein. There may also be interactions between these pathways.

The presence of neuropathy is associated with significant morbidity, including:

- recurrent foot infections and ulceration, possibly leading to amputation;
- impotence in diabetic men;
- sudden death in individuals with cardiovascular autonomic neuropathy.

Screening strategies

Cardiovascular autonomic neuropathy may be detected by testing heart rate control in response to deep breathing (paced respiration) or after standing from the lying position, and/or the circulatory response to the Valsalva manoeuvre. This may be important as a screen before a patient undergoes general anaesthesia, since those with cardiovascular autonomic neuropathy have an increased mortality risk from such a procedure.

A simple screening procedure for distal sensory-motor neuropathy includes:

- inspection of the feet for evidence of dry skin, hair or nail abnormalities, callus or infection;
- the grading of vibratory sensation at the dorsum of the toe as normal, reduced or absent;
- the grading of ankle reflexes as normal, reduced or absent.

Patients with abnormalities should undergo a more complete neurological assessment.

Intervention strategies

Realistic objectives must be chosen for any programme designed to prevent the onset or progression of diabetic neuropathy. In the early stage of distal sensory-motor neuropathy, the goals are early detection, halting disease progress and minimizing further deterioration. In the symptomatic stage, they include symptom assessment, halting disease progression, relief of symptoms, preventing further deterioration, and allowing nerve repair and regeneration. In the severe stage, they include management of clinical

symptoms, helping patients to overcome disability and learn to have a limited expectation of full return of function, and preventing further deterioration and ulceration.

The frequency, severity and progression of neuropathy are related to the degree and duration of hyperglycaemia, and may also be a function of age. Several randomized studies have suggested that manifestations of neuropathy may be stabilized or improved by improved glucose control [27].

Aldose reductase inhibitors are now available in an increasing number of countries. They offer the potential for inhibiting the polyol pathway, one of the pathways thought to lead to diabetic neuropathy. Other interventions aimed at altering the pathophysiology of neuropathy are under evaluation. Symptomatic and supportive treatments are also necessary to reduce the burden imposed by diabetic neuropathy.

There should be early identification of those patients at risk of developing neuropathic foot problems and appropriate education should be given [22,23]. Foot ulceration and amputation in diabetic patients will be looked at in detail in the following section.

Potential obstacles to prevention include:

- lack of awareness of the limb-threatening and disabling nature of diabetic neuropathy because the disorder is asymptomatic in its early stages;
- lack of awareness among primary care physicians of the benefits of timely detection and treatment;
- primary care physicians' lack of necessary skills in detecting neuropathy;
- lack of economic resources to seek care;
- lack of neurologists to evaluate neuropathy quantitatively, e.g. by neuro-physiological testing;
- lack of realistic appreciation that interventions may halt progression but not necessarily reduce symptoms;
- feelings of hopelessness on the part of patients and health care providers [27–30].

Needs

There is a need:

- for data on the current prevalence of neuropathy and the continued collection of such data for monitoring the effectiveness of interventions;
- to ensure the training of those who will educate patients and primary care physicians;
- to ensure the availability of neurologists to evaluate neuropathy;
- to educate patients and primary care physicians about the benefits and need for detection and treatment of neuropathy;

- to achieve good glycaemic control in an attempt to minimize the development of neuropathy;
- to reduce the economic barriers preventing patients from seeking appropriate care when needed.

Monitoring and evaluation

Monitoring and evaluation should include:

- objective programmes for educating and testing the knowledge of primary care physicians;
- evaluation of patients' knowledge about diabetic neuropathy and recommended care both before and after educational programme;
- evaluation of the success of programmes by monitoring changes in behaviour;
- monitoring the cost-effectiveness of such programmes.

Conclusions

The highest priority at present is the education of patients and their physicians about the potential for detection and treatment of early neuropathy. Large scale studies have shown that glycaemic control is beneficial in reducing the frequency of progression of neuropathy. Further studies to investigate the usefulness of therapeutic agents such as aldose reductase inhibitors should be encouraged, given that other current modes of therapy, apart from improved metabolic control, are purely symptomatic and do not influence the cause of the neuropathy.

Neuropathic foot

Background

More hospital beds are occupied by diabetic patients with foot problems than by those with all other consequences of diabetes. The problem of limb amputation in people with diabetes is of such a serious and global nature that a special section giving guidelines for prevention was felt to be warranted in this publication [22,23].

Diabetes is associated with increased frequency of lower-limb amputations, many of which are potentially preventable. Epidemiological data suggest that >50% of the 120 000 non-traumatic lower-limb amputations in the United States of America are associated with diabetes and that the overall risk of amputation in people with diabetes is 15 times that in people without diabetes.

The underlying lesions that often result in chronic ulceration and amputation have been termed the diabetic foot. This is defined as infection, ulceration and destruction

of deep tissues, associated with neurological abnormalities (loss of pain sensation) and various degrees of peripheral vascular disease in the lower limb. A number of preventive strategies (careful self-examination, specially fitted shoes, minimization of trauma, etc.) alongside earlier detection and more aggressive management of foot ulcers (e.g. local debridement, provision of special supports and early antibiotic therapy) will prevent or delay lower-limb amputations. In developing countries, lack of proper footwear and inadequate hygiene, together with poorly controlled diabetes, are major causes of lower-limb amputations.

Studies have shown the financial benefit of prevention of amputation. Hospitalization for treatment of infection and/or amputation may often last several weeks. Ambulatory care and education may therefore save substantial amounts of money.

Screening strategies

The key to success in managing the diabetic foot is to organize a regular screening programme to identify all patients at risk of developing foot ulcers. Physicians should examine the feet of diabetic patients on a regular basis. In some situations it may be helpful to create a registry (adapted, if possible, to the local health care system) of all people with diabetes so that they may be called for regular screening and identified if they are at risk. Patients at risk should be seen regularly and should expect their physicians to perform regular foot examinations [22].

Screening can be carried out by adequately trained observers and without complex technology. Simple classification schemes may be of value in identifying risk. Patients at particular risk will exhibit one or more of the following features, assessed by simple enquiry and clinical examinations:

- a past history of foot ulcer;
- symptoms of neuropathy (tingling and decrease or loss of the sense of pain and touch) and/or ischaemic vascular disease (exercise-induced calf pain or cold feet);
- signs of neuropathy (warm feet, non-sweating skin, wasted muscles, clawed toes, hard skin over pressure points, bounding pulses or venous distension) and/or peripheral vascular disease (cold feet, shiny and thinned skin, absent pulses or atrophy of subcutaneous tissue);
- severe foot deformities in the presence of less severe neuropathy and/or peripheral vascular disease;
- other long-term complications of diabetes (renal failure, significant ocular involvement);
- other risk factors (decreased visual acuity, orthopaedic problems interfering with the correct care of the feet, such as arthritis of knee, hip or spine, poor footwear);
- personal factors (low socioeconomic status, being elderly or socially isolated, psychological attitudes of denial) [22,23].

Intervention strategies

For the neuropathic foot, facilities for electrophysiological study and the quantitative assessment of vibration and thermal threshold are important in research and differential diagnosis, but not in routine clinical practice. Simple tools, such as the graduated tuning fork and standard monofilament, are useful for the semi-quantitative diagnostic evaluation of neuropathy. Wherever possible, diabetic patients who have significant vascular disease and ischaemia of the foot should have access to the modern investigative techniques of Doppler ultrasonography and arteriography. Non-invasive angioplasty or surgical arterial reconstruction should be performed if indicated. If angiography is to be performed, special attention should be paid to patients with nephropathy, even in its early stages, since radiopaque dye administration can provoke renal deterioration. Appropriate hydration before the procedure is often necessary [21,22].

In the treatment of established foot ulcers, early local debridement and aggressive antibiotic therapy should be considered. For resistant foot ulcers, special plantar supports or castings should be provided. Patients need to understand the importance of adhering strictly to the prescribed antibiotic regimen. Every member of the diabetes care team should understand and practice the principles of foot protection.

A specialist foot-care team should be part of every comprehensive diabetes care service. The foot-care team should consist of a physician, a nurse specialist or educator, and a chiropodist or podiatrist. In addition, the team should ideally have easy access to:

- a podiatrist debridement;
- a vascular radiologist with facilities for non-invasive intra-arterial angioplasty;
- a vascular surgeon to offer reconstruction;
- an orthopaedic surgeon to correct severe structural abnormalities;
- physiotherapists for the rehabilitation of patients after amputation; because of their age, usually >55 years, and associated long-term complications (visual problems, postural hypotension, etc.) the rehabilitation period is often several months long.

If no specialists are available, experienced general practitioners and home visiting nurses can manage at least two-thirds of cases, providing they have received 1 or 2 days formal training.

Currently, many of the above health professionals and services are still unavailable in developing countries, where they are most needed. In this event, training of non-specialist health workers and simple direct instructions to patients themselves are likely to reduce the risk of serious tissue destruction. As with other diabetic complications, the frequency of follow-up of foot complications will depend on their type and severity. For instance, patients with plantar ulcers should be seen at short intervals (1–3 weeks); those with loss of pain sensation but without local lesions may be seen every 3 months [23].

Education

Education is the most important contribution to the prevention of foot lesions in diabetes [22,23]. The first objective should be to increase the knowledge of all those who care for diabetic patients concerning the dangers inherent in the development of diabetic foot lesions and the different skills needed to examine feet and to treat lesions.

Another goal is to establish an educational programme for patients at special risk of developing foot ulcers. The programme should include:

- regular attendance by patients for the reinforcement of knowledge and motivation for continuing to care for their feet;
- formal teaching sessions to explain the reasons for the vulnerability of the diabetic foot, and the importance of everyday matters such as suitable footwear and foot hygiene;
- the provision of appropriate written and/or audiovisual material.

Education of patients has to be centred on appropriate skills aimed at preventing foot lesions. Patients should learn:

- not to walk bare-footed;
- to examine shoes daily and look for foreign bodies;
- to avoid “bathroom surgery” (no scissors, no razor blades, no chemical skin loosener for hyperkeratosis);
- to treat fungus disease and minor cuts early;
- to use a mirror to observe the plantar surface of the foot;
- to test the degree to which pain sensation has been lost;
- to prevent burns (no hot water or electric heaters).

Chapter 10

Prevention of diabetes

Background

The implementation of a national diabetes programme should address primary, secondary and tertiary prevention. While there is not yet conclusive evidence to suggest that type 1 diabetes mellitus can be prevented, primary prevention of type 2 is possible. Primary prevention has an impact by reducing both the need for diabetes care and the need to treat diabetic complications [32,45].

Secondary and tertiary preventions are key to reducing the risk of costly diabetic complications, as well as their associated disabilities. There is great potential for tertiary prevention in diabetes, especially with regard to blindness, limb amputation and adverse pregnancy outcomes. Rehabilitation and special assistance are required for those who do develop disabling complications. Overall, action taken early in the course of diabetes is more beneficial in terms of quality of life as well as being more cost-effective, especially if this action can prevent hospital admission.

Many barriers exist at the prevention level, including:

- lack of knowledge and awareness by individuals and communities;
- inadequately trained personnel in the preventive health care field;
- inadequate use of media for creating awareness for health education;
- changing of deeply-rooted lifestyles is very difficult;
- social problems [45].

Primary prevention

Lifestyle changes aimed at weight control and increased physical activity are important objectives in the prevention of type 2 diabetes mellitus. The benefits of reducing body weight and increasing physical activity are not confined to type 2 diabetes, they also play a role in reducing heart disease and high blood pressure. Lifestyle is the key to reversing these trends. Ministries of health, other ministries and the private sector need to have a commitment to a healthy lifestyle in order to reduce the risk of type 2 diabetes and its complications developing in populations. The management of high blood pressure and raised blood lipids is equally important [45,46].

Randomized controlled trials have shown that in subjects at high risk for developing type 2 diabetes mellitus (e.g. those with IGT, IFG) the adoption of favourable lifestyle changes brings about a significant reduction in the incidence of type 2. The Da Quing Study from China [30] showed that diet and exercise alone or in combination in patients with IGT led to a 31%–46% reduction in the risk of diabetes mellitus over a follow-up period of 6 years. A study conducted in Finland by Tuomilehto et al. [33] in individuals with IGT showed that the incidence of type 2 diabetes was 23% in the control group compared to 11% in the intervention group (exercise and diet modifications) over a 4-year period.

The Diabetes Prevention Programme Research Group [34], randomly assigned 3234 non-diabetic subjects (mean age 51 years, mean body mass index 34.0 kg/m^2) with elevated fasting and post-load plasma glucose concentrations to either placebo, metformin (850 mg twice daily), or a lifestyle modification programme. The objective was to achieve at least a 7% weight loss and at least 150 minutes of physical activity per week. The incidence of type 2 diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively.

Community awareness and primary prevention

The above studies highlight the importance of physical inactivity and unhealthy diets as strong risk factors for diabetes mellitus. A reasonable exercise programme and a modest amount of weight loss led to a marked decrease in diabetes incidence by more than 50%.

Due to the importance of the prevention of type 2 diabetes and its complications, Eastern Mediterranean countries should give priority to the development of community-based healthy lifestyle programmes that focus on:

- maintaining a ‘healthy’ weight [35];
- an active lifestyle which includes regular physical activity;
- early identification of subjects at risk of developing type 2 diabetes mellitus;
- identifying subjects at high risk of noncommunicable diseases, such as hypertension, diabetes and heart disease;
- optimal maternal nutrition and weight maintenance;
- introduction of healthy lifestyle programmes in the early school years. These should focus on the prevention of risk factors, which will predispose to noncommunicable diseases in later life;
- cessation of smoking.

Secondary prevention

The primary purpose of secondary prevention activities such as screening is to identify individuals without symptoms who already have the disease, are at high risk of developing complications related to the primary disease, and where intervention could have a beneficial effect. Secondary prevention is the key to reducing the risk of costly and disabling diabetic complications. There is now conclusive evidence that good control of blood glucose levels can substantially reduce these complications. The United Kingdom Prospective Diabetes Study group [27,28] have proven that the risk of diabetic complications can be reduced significantly in people with type 2 diabetes. It showed that:

- with good glucose control, diabetes-related complications (such as blindness, stroke, renal disease, limb amputation and heart attack) can be reduced by 12%.
- with good blood pressure control, diabetes-related complications can be reduced by 24%, and diabetes-related deaths by up to 32%.

The Diabetes Control and Complications Trial [29] in the USA had similar findings for blood glucose control in type 1 diabetes.

Therefore, action taken early in the course of diabetes is more beneficial in terms of quality of life and is more cost-effective, especially if this action can prevent hospital admission. The management of high blood pressure and raised blood lipids (fats) is equally important.

Tertiary prevention

Tertiary prevention of diabetes includes every action taken to prevent or delay the consequences of diabetic complications, such as blindness, foot amputation and adverse pregnancy outcomes. Strategies for tertiary prevention involve prevention of the development of complications by strict metabolic control, education and effective treatment. They also involve screening for early stages of complications, when intervention and treatment are generally more effective. Such screening for complications aimed at early intervention and treatment has proved successful and may be even more effective than strategies aimed at preventing the development of complications. As an example, the introduction of laser photocoagulation in the treatment of retinopathy has led to a dramatic decrease in diabetes-related blindness. Rehabilitation of persons with diabetic complications is essential since many individuals with diabetes may develop disabling complications with high associated costs.

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Annex 1

Regional consultation on diabetes prevention and control

Teheran, Islamic Republic of Iran, 2–5 February 2005

Participants in the Regional Consultation on Diabetes Prevention and Control, Teheran, Islamic Republic of Iran, 2–5 February 2003, recognized the importance of diabetes and its complications and the need to strengthen data collection. They recommended that diabetes be established as a health priority in the current and future national programmes/plans, and that Member States establish secondary prevention activities, such as screening, in order to identify asymptomatic individuals who have diabetes and are at risk of developing complications. They also recommended that diabetes education be promoted in its various forms and methods within the framework of a national diabetes control programme, targeting the individual family and community, and that community-based healthy lifestyles programmes be developed which focus on maintenance of normal weight, an active lifestyle which includes regular physical activity and cessation of smoking.

The participants recommended an integrated approach to prevention and care of diabetes mellitus. Countries of the WHO Eastern Mediterranean Region are urged to implement the following strategies.

1. Promotion of healthy lifestyle

Political commitment is necessary to advocate and promote a healthy lifestyle for the community that will reduce the risk of developing type 2 diabetes mellitus or diabetes complications.

2. Raising community awareness (Eat less–Walk more)

Since obesity is the major risk factor, not only for diabetes, but also for hypertension and cardiovascular diseases, it is essential to create awareness in the community about diabetes, the risk factors involved and the importance of a healthy lifestyle, including intake of fewer calories and more physical activity.

3. Primary prevention of diabetes

Primary prevention is the prevention of the onset of diabetes itself and will have an impact by reducing both the need for diabetes care and the need to treat diabetic complications. This necessitates establishing national strategies for primary prevention.

4. Screening for type 2 diabetes mellitus

In view of the increasing evidence that type 2 diabetes mellitus can be prevented, it is essential to give priority to the early identification of people at risk as well as those who are at high risk of hypertension and coronary artery diseases.

5. Establishment of a regional training course for diabetes educators

A regional course for diabetes educators is advocated to provide training that will include integration of current diabetes care practices, and teaching and learning principles. It will employ a flexible approach to teaching, and respect for lifestyle and health beliefs. For such a course to be successful the concept of the diabetes educator needs to be established as part of diabetes management in countries of the Region.

6. Development of a national strategy

Management of diabetes needs to be monitored through implementation of national strategies for optimal control of diabetes, hypertension, dyslipidaemia and obesity.

The participants in the consultation were:

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