

Chapter II: Diabetes Mellitus

Definition

Diabetes mellitus (DM) is defined as a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, protein, and fat metabolism resulting from defects in insulin secretion, insulin action, or both.

Classification

1. Type I diabetes

- A. Immune mediated
- B. Idiopathic

- Formerly known as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes mellitus, is caused by autoimmune destruction of the β -cells of the pancreas, rendering the pancreas unable to synthesize and secrete insulin.
- It usually occurs before the age of 30, has a short asymptomatic period, and runs a severe clinical course.

2. Type II diabetes

- Formerly known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, results from a combination of insulin resistance and inadequate insulin secretion.
- Onset is usually after the age of 30 years and the prevalence increases with age.

3. Other specific types

- A. Genetic defects of β -cell function
- B. Genetic defects in insulin action
- C. Diseases of the exocrine pancreas
- D. Endocrinopathies
- E. Drug- or chemical-induced
- F. Infections
- G. Uncommon forms of immune-mediated diabetes (IMD)
- H. Other genetic syndromes sometimes associated with diabetes

4. Gestational Diabetes Mellitus (GDM)

Risk Factors

- o **Individuals at high risk of DM include:**
 - Obese men and women over 40 years.
 - Family history of DM.
 - Previous GDM or impaired glucose tolerance (IGT).
- o **Risk factors for GDM include:**
 - Obesity.
 - Increased maternal age.
 - Glucosuria.
 - Family history of diabetes.

Burden

- **Prevalence of DM is 9.3% of Egyptian adults (≥ 20 years).**
- **Complications:**
 - o Risk factor for:
 - Coronary heart disease.
 - Cerebrovascular disease.
 - Nephropathy and renal failure.
 - o Life-threatening metabolic complications.
 - o Polyneuropathy.
 - o Nontraumatic amputations.
 - o Blindness.

Screening test

Measurement of fasting plasma glucose (FPG).

Diagnosis

- o **Diagnosis of diabetes is based on:**
 - Typical symptoms of DM (polyurea, polydipsia, and weight loss).
 - Fasting plasma glucose > 126 mg/dL (7 mmol/L).
 - 2-h postload plasma glucose > 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT).
 - Casual (random) plasma glucose > 200 mg/dL (11.1 mmol/L).
- o If any one of the above criteria is met, confirmation on a subsequent day is necessary to establish the diagnosis.
- o Repeat testing is not needed in hyperglycemic patients with acute metabolic decompensation.

Burden of Suffering

Prevalence in Egypt¹

- o Prevalence of DM is 9.3% of Egyptian population (≥ 20 years).
- o Prevalence of diagnosed diabetes in Egyptian population (≥ 20 years) is:
 - 2.4% of rural residents.
 - 8.4% of lower socioeconomic status urban residents.
 - 10.0% of higher socioeconomic status urban residents.
- o The estimated number of persons with diagnosed and undiagnosed diabetes is:
 - 3.24 million in 1995.
 - 3.80 million in 2000.
 - 8.80 million in 2025.

Complications

- o Risk factor for:^{3,6,7}
 - Coronary heart disease (leading cause of death worldwide).
 - Cerebrovascular disease.
 - Nephropathy and renal failure (leading cause of end stage renal failure worldwide).
- o Compared to persons without diabetes, diabetic patients have:^{2,11}
 - Higher hospitalization rate.
 - Longer hospital stays.
 - Increased ambulatory care visits.
- o Life-threatening metabolic complications.
- o Most common cause of polyneuropathy, with approximately 50% of diabetics affected within 25 years of diagnosis.⁴
- o Leading cause of nontraumatic amputations.⁵
- o Leading cause of blindness in adults (20-74 years).⁸
- o Infants of diabetic mothers are at increased risk of:^{9,10}
 - Fetal malformation.
 - Prematurity.
 - Spontaneous abortions.
 - Macrosomia (birth weight above 4-4.5 Kg), which is associated with increased risk of:¹²⁻¹⁵
 - Operative delivery.
 - Birth trauma.
 - Shoulder dystocia.
 - Metabolic derangements (as hyperbilirubinemia, hypoglycemia).
- o Women with a history of GDM are also at risk for developing NIDDM later in life.¹⁶

Diagnosis of Diabetes Mellitus¹⁷

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Impaired glucose tolerance (IGT)

- o Impaired glucose tolerance (IGT) is an intermediate form of disordered glucose metabolism based on intermediate results of the OGTT (see later).
- o Patients with IGT are at increased risk of developing frank diabetes, but rates of progression are highly variable.
- o IGT is also a risk factor for cardiovascular disease.¹⁸
- o A significant number of individuals diagnosed with IGT revert to normal on repeat testing,¹⁸ and the treatment implications of IGT alone are uncertain.

Glucose

Diagnosis/Screening

- o The disordered carbohydrate metabolism that underlies diabetes manifests as hyperglycemia. Therefore, measurement of plasma glucose is the sole diagnostic criterion.
 - Although included as a criterion, the oral glucose tolerance test (OGTT) was not recommended for routine clinical use in nonpregnant individuals (see below).
- o Population screening for type 2 diabetes, previously controversial, is now recommended for those at risk of developing the disease. Screening is recommended for several reasons:
 - The onset of type 2 diabetes is estimated to occur 4–7 years before clinical diagnosis, and epidemiologic evidence indicates that complications may begin several years before clinical diagnosis.
 - Furthermore, at least 30% of people with type 2 diabetes are undiagnosed.
- o FPG should be measured in all asymptomatic people 45 years of age. If results are <6.1 mmol/L (110 mg/dL), testing should be repeated at 3-year intervals.
- o Because of the increasing prevalence of type 2 diabetes in children, screening of children has been suggested recently.
- o Starting at age of 10 years, testing should be performed every 2 years in overweight individuals who have two other risk factors, namely family history, race/ethnicity, and signs of insulin resistance.

- o Despite these recommendations, there is no published evidence that treatment based on screening has value.

Monitoring/Prognosis

- o Although there is evidence linking high plasma glucose concentrations to adverse outcome, substantially more data are available that directly correlate increased glycated hemoglobin (GHb) with complications of diabetes.
- o Routine measurement of plasma glucose concentrations is not recommended as the primary means of monitoring or evaluating therapy in individuals with diabetes.
- o Laboratory plasma glucose testing can be used to supplement information from other testing, to test the accuracy of self-monitoring, or when adjusting the dose of oral hypoglycemic agents. In addition, individuals with well-controlled type 2 diabetes who are not on insulin therapy can be monitored with periodic measurement of FPG.
- o There is a direct relationship between the degree of plasma glucose control and the risk of renal, retinal, and neurological complications. This correlation has been demonstrated for type 1 and more recently for type 2 DM.
- o Persons with type 1 and type 2 diabetes who maintained lower average plasma glucose concentrations exhibited a significantly lower incidence of microvascular complications (namely diabetic retinopathy, nephropathy, and neuropathy) but no significant difference was detected for macrovascular disease (myocardial infarction or stroke).

Analytical considerations

Preanalytical

- o Blood for fasting plasma¹ glucose analysis should be drawn after the individual has fasted overnight [no caloric intake for at least 8 h, during which time the individual may consume water ad libitum].
- o Plasma should be separated from the cells within 60 min; if this is not possible, a tube containing a glycolytic inhibitor such as sodium fluoride should be used for collecting the sample.
- o Recent evidence revealed a diurnal variation in FPG, with mean FPG higher in the morning than in the afternoon, indicating that many cases of undiagnosed diabetes would be missed in patients seen in the afternoon.

Meters

- o Self-monitoring of blood glucose (SMBG) is recommended for all insulin-treated patients with diabetes.
- o For type 1 patients, SMBG is recommended three or more times a day. SMBG may be desirable in patients treated with sulfonylurea or other insulin secretagogues and in all patients not achieving goals.
- o In patients with type 2 diabetes, SMBG may help achieve better control, particularly when therapy is initiated or changed. However, there are no data to support this concept.

¹ Glucose concentrations in plasma are 11% higher than whole blood if the hematocrit is normal. Glucose concentrations in heparinized plasma are reported to be 5% lower than in serum.

Oral Glucose Tolerance Test (OGTT)

- o The OGTT, once the gold standard for diagnosing diabetes mellitus, is now not recommended by the ADA for diagnosing either type 1 or 2 diabetes, but it continues to be recommended in a limited fashion by the WHO [when the FPG concentration is in the IFG range [6.1 mmol/L-7.0 mmol/L (110–126 mg/dL)].
- o The 2-h glucose tolerance test is recommended for the diagnosis of GDM by both the ADA and WHO.

Interpretation

- o After 3 days of unrestricted diet and an overnight fast (8–14 h), FPG is measured, followed by the oral ingestion of 75 g of anhydrous glucose in 250–300 mL of water over 5 min. For children, the dose is 1.75 g glucose/kg up to 75 g of glucose.
- o Blood samples are collected 2 h after the load, and plasma glucose is analyzed.

	Zero hour	2 hours
Impaired fasting glucose (IFG)	> 110 mg/dL (6.1 mmol/L) to < 126 mg/dL (7.0 mmol/L)	< 140 mg/dL (7.8 mmol/L)
Impaired glucose tolerance (IGT)	< 126 mg/dL (7.0 mmol/L)	≥ 140 mg/dL (7.8 mmol/L) to ≤ 200 mg/dl (11.1 mmol/L)
Diabetes mellitus (DM)	≥ 126 mg/dL (7 mmol/L)	≥ 200 mg/dl (11.1 mmol/L)

*Any single abnormal value should be repeated on a separate day.

Urinary Glucose

- o Semiquantitative urine glucose testing, once the hallmark of diabetes care in the home setting, has now been replaced by SMBG.
- o Semiquantitative urine glucose monitoring should be considered only for patients who are unable to or refuse to perform SMBG because urine glucose concentration does not accurately reflect plasma glucose concentration.

Noninvasive or Minimally Invasive Glucose Analyses

- o Noninvasive glucose analyses cannot be recommended as replacements for SMBG or glucose measurements by a laboratory.
- o Currently, there are only two devices that have been approved by the Food and Drug Administration (FDA) for noninvasive or minimally invasive glucose sensing:
 - the Gluco Watch Biographer (Cygnum), and
 - the Continuous Glucose Monitoring System (MiniMed).
- o Although promising, routine use of these devices cannot be recommended at this time because clinical studies remain limited.

Ketone Testing

- o Determinations of ketones in urine and blood are widely used in the management of patients with diabetes mellitus as adjuncts for both diagnosis and ongoing monitoring of DKA.

- o All patients with diabetes mellitus should test their urine for ketones during acute illness, stress, persistent hyperglycemia [plasma glucose >16.7 mmol/L (300 mg/dL)] pregnancy, or symptoms consistent with DKA (nausea, vomiting, or abdominal pain).

Glycosylated Hemoglobin (GHb)

- o GHb is a clinically useful index of mean glycemia^{II} during the preceding 120 days, the average life span of erythrocytes.
- o Concentrations of other blood-based glycosylated proteins (e.g., glycosylated serum/plasma proteins, and fructosamine) also reflect mean glycemia, but over a much shorter time than GHb: 15–30 days and 60–120 days, respectively.
- o GHb testing should be performed at least biannually in all patients and quarterly for patients whose therapy has changed or who are not meeting treatment goals. Treatment goals are to maintain GHb concentrations <7% and reevaluation of the treatment regimen for GHb values >8%.

Genetic Markers

- o Type 1 diabetes: Routine measurement of genetic markers is not of value at this time for the diagnosis or management of patients with type 1 diabetes. For selected diabetic syndromes, valuable information can be obtained with definition of diabetes-associated mutations.
- o For immune-mediated (type 1A) diabetes (IMD), HLA typing can indicate absolute risk of diabetes, as extended by insulin (INS) gene typing, and can assist in assigning a probability of the diagnosis of IMD to diabetes of uncertain etiology. It is possible to screen newborn children to identify those at increased risk of developing IMD. Screening cannot be recommended until there is an intervention available to delay or prevent the disease.
- o Type 2 diabetes and maturity onset diabetes of youth (MODY): There is no role for routine genetic testing and these studies should be confined to the research setting and evaluation of specific syndromes.

Autoimmune Markers

- o IDDM is a genetically linked autoimmune disorder, in which progressive destruction of insulin-producing pancreatic islet cells eventually leads to complete dependence on exogenous insulin.²⁷
- o Islet cell autoantibodies and insulin autoantibodies are present in the majority of patients with newly diagnosed IDDM,²⁸ and may precede the onset of clinical symptoms by months to years.
- o The potential value of immune markers is greater in high-risk individuals (i.e., first-degree relatives of affected patients). A combination of immune markers and measures of insulin responsiveness can identify a population at very high risk (up to 70%) of developing IDDM.²⁸⁻³⁰
- o No therapeutic intervention has been identified that will prevent diabetes. Therefore, although several autoantibodies have been detected in individuals with type 1 diabetes,

^{II} Each 1% change in GHb is related to a change in mean plasma glucose of 2 mmol/L (35 mg/dL).

islet cell autoantibodies are not recommended for routine diagnosis of diabetes or for screening.

- o Islet cell autoantibodies are recommended for screening of nondiabetic family members who wish to donate part of their pancreas for transplantation to a relative with end stage, immune-mediated (type 1) diabetes.

Microalbuminuria

Diagnosis/Screening

Definition of microalbuminuria and overt nephropathy:

	mg/24h	µg/min	µg/mg CR
Normal	<30	<20	<30
Microalbuminuria	30-300	20-200	30-300
Clinical albuminuria “Overt Nephropathy”	>300	>200	>300

- o Diabetes is the leading cause of end-stage renal disease.
- o Early detection of diabetic nephropathy relies on tests for urinary excretion of albumin.
- o Conventional qualitative tests (chemical strips or dipsticks) for albuminuria do not detect the small increases in urinary albumin excretion seen in early stages of nephropathy. For this purpose, tests for "microalbuminuria" are used.
- o Quantitative measurement of urine protein excretion is used in the assessment of the severity of proteinuria and its progression, in planning treatment, and in determining the impact of therapy.
- o Annual microalbuminuria testing of patients without clinical proteinuria should begin in pubertal or postpubertal individuals 5 years after diagnosis of type 1 diabetes and at the time of diagnosis of type 2 diabetes.

Prognosis

- o Microalbuminuria has prognostic significance:
 - In 80% of people with type 1 diabetes and microalbuminuria, urinary albumin excretion increases at a rate of 10–20% per year, with development of clinical proteinuria (>300 mg albumin/day) in 10–15 years. After development of clinical grade proteinuria, most (>80%) patients go on to develop decreased glomerular filtration rate and, given enough time, end-stage renal disease.
 - In type 2 diabetes, 20–40% of patients with microalbuminuria progress to overt nephropathy, but by 20 years after overt nephropathy, only 20% develop end-stage renal disease.
 - In addition, patients with diabetes (type 1 and 2) and microalbuminuria are at increased risk for cardiovascular disease.

Miscellaneous Potentially Important Analytes

Insulin and precursors

- o There is no role for routine testing for insulin, C-peptide, or proinsulin in most patients with diabetes.

- o Differentiation between type 1 and type 2 diabetes may, in most cases, be made based on the clinical presentation.
- o There is no role for measurement of insulin concentration in the diagnosis of the metabolic syndrome because knowledge of this value does not alter the management of these patients.
- o These assays are useful primarily for research purposes and, in rare cases, to identify patients with an absolute requirement for insulin before switching to oral agents, or to assist patients in obtaining insurance coverage for continuous subcutaneous infusion pumps.

Amylin

- o Amylin is co-secreted and co-located with insulin by the pancreatic β cells in response to nutrient intake.
- o Amylin helps to regulate glucose metabolism by delaying gastric emptying and decreasing glucagon production.
- o Assays for amylin are not clinically useful in the management of diabetes and should be confined to research.

Leptin

- o Leptin is an amino-acid protein synthesized by adipose tissue and plays a role in regulating appetite and energy intake via the hypothalamus, as well as influencing thermogenesis and reproductive functions.
- o Its routine measurement is not of value at this time for the evaluation or management of patients with diabetes or obesity.

Lipids

- o All adults with diabetes should receive annual lipid profiles.
- o Individuals at low risk, i.e., those with LDL <2.6 mmol/L (100 mg/dL) and HDL >1.15 mmol/L (45 mg/dL) for men and >1.4 mmol/L (55 mg/dL) for women, may be screened less frequently.
- o Because many patients with diabetes are candidates for lipid-lowering therapy, more frequent measurements may be required until control is achieved.

New cardiovascular risk factors

- o Measurement of nontraditional cardiovascular risk factors, such as C-reactive protein, fibrinogen, apolipoprotein (apo) B, and homocysteine, is not recommended for routine assessment of risk in patients with diabetes because the results would not lead to changes of therapy.
- o Should ongoing trials support the use of folic acid to lower CAD by lowering homocysteine concentrations, or the use of other specific therapies aimed at one or more nontraditional risk factors, this recommendation may change.

Gestational Diabetes Mellitus (GDM)

- o GDM is defined as development of glucose intolerance during pregnancy.
- o It is recommended to screen pregnant women at 24- 28 weeks of gestation.¹⁹
- o In an unselected pregnant population (prevalence of GDM approximately 3%), fewer than one in five women with a positive glucose challenge test will meet criteria for gestational diabetes on a full OGTT.²²
- o The elevations in plasma glucose in GDM are less pronounced than in IDDM or NIDDM. As a result, neither serum glycosylated proteins^{21,23-26} nor urine glucose²⁰ are sufficiently sensitive for detecting GDM.
- o The ADA modified their recommendations for laboratory diagnosis of GDM in 2000. Their guidelines are:
 1. Low-risk patients require no testing. Low risk status is limited to women meeting all of the following:
 - Age <25 years
 - Weight normal before pregnancy
 - Member of an ethnic group with a low prevalence of GDM
 - No known diabetes in first-degree relatives
 - No history of abnormal glucose tolerance
 - No history of poor obstetric outcome
 2. Average-risk patients (patients who fall between low and high risk) should be tested at 24–28 weeks of gestation.
 3. High-risk patients should undergo immediate testing. They are defined as having any of the following:
 - Marked obesity
 - Personal or strong family history of GDM
 - Glucosuria
- o The first step in laboratory testing is identical to that for diagnosing type 1 or 2 diabetes, i.e., a FPG ≥ 7.0 mmol/L (126 mg/dL) or a casual plasma glucose ≥ 11.1 mmol/L (200 mg/dL) confirmed on a subsequent day. However, if the above tests are normal, the ADA recommends that average- and high-risk patients receive a glucose challenge test following one of two methods:
 - One-step: Perform either a 100-g or 75-g OGTT. Two or more of the venous plasma glucose concentrations indicated in the following table must be met or exceeded for a positive diagnosis.

Criteria for interpreting 100-gm OGTT		
	mmol/L	mg/dL
Fasting	5.3	95
1h	10	180
2h	8.6	155
3h	7.8	140

- Alternatively, a 75-g OGTT can be performed, but it is not as well validated as the 100-g test. In the 75-g test, diagnostic criteria for plasma glucose values are the same as for the 100-g test, except that there is no 3-h measurement. Two or more of the plasma glucose values must equal or exceed the cutoffs to diagnose GDM.

- Two-step: The first step is a 50-g oral glucose load (the patient does not need to be fasting), followed by a plasma glucose determination at 1 h. A plasma glucose value ≥ 7.8 mmol/L (140 mg/dL) indicates the need for definitive testing. A value ≥ 7.2 mmol/L (130 mg/dL) may be used because it will detect ~10% more diabetic patients. The second and definitive test is one of the two OGTT described above.

Effectiveness of Early Detection

Asymptomatic NIDDM

- o Up to 20% of patients with newly diagnosed NIDDM already have early retinopathy and/or nephropathy, suggesting that the onset of diabetes may be many years (estimated 9-12 years) before clinical diagnosis, and that the microvascular changes may precede overt symptoms in many patients.³¹
- o The degree of hyperglycemia and duration of disease are associated with microvascular complications. Earlier detection through screening might provide an opportunity to reduce the progression of microvascular or macrovascular disease due to asymptomatic hyperglycemia.
- o There is little direct evidence of a benefit of detecting and treating IGT.^{32,33} Untreated, most persons with IGT do not develop diabetes, but the reported cumulative incidence of diabetes at 10 years has varied from 15% to 61%.

Persons at Risk for IDDM

- o Earlier diagnosis of IDDM could be of considerable benefit if treatment could arrest the disease process before severe insulinopenia and hyperglycemia had developed.
- o Immunosuppressive can delay disease progression in some patients with new-onset IDDM, but the benefit has not been sustained in most patients, and the serious adverse effects of immunosuppressive agent are likely to preclude their use in completely asymptomatic persons.

GDM complications

- o Degrees of hyperglycemia more subtle than in GDM may result in increased maternal and neonatal complication rates.³⁴⁻³⁶
- o The incidence of macrosomia and preeclampsia/eclampsia is higher in women who demonstrate at least one abnormal result among the four points on a glucose tolerance test.
- o Although treatment of GDM can reduce macrosomia, the impact of widespread screening and treatment on the overall incidence of macrosomia and dystocia may be quite small.

Management³⁷

1. Screening recommendations for diabetic patients

CHILDREN AND YOUNG PEOPLE	<ul style="list-style-type: none">o Patients with cystic fibrosis should be screened annually for diabetes from 10 years of age.o All people with diabetes should be annually screened for the following from the age of 12 years:<ul style="list-style-type: none">- Retinopathy- Microalbuminuria- Blood pressureo Young people should be screened for thyroid and coeliac disease at onset of diabetes and at intervals throughout their lives.
RENAL	<ul style="list-style-type: none">o All patients with diabetes should have their urinary albumin concentration and serum creatinine measured at diagnosis and annually.
VISUAL IMPAIRMENT	<ul style="list-style-type: none">o Systematic screening for diabetic retinal disease should be provided for all people with diabetes.o Patients with type 2 diabetes should be screened from diagnosis.o Patients with type 1 diabetes should be screened at age 12 years or at onset of puberty whichever is first.o Retinal photography or slit lamp biomicroscopes should be used in a programme of systematic screening.o Dilated direct ophthalmoscopy should be used for opportunistic screening.
FOOT DISEASE	<ul style="list-style-type: none">o All patients with diabetes should be screened for foot disease.

2. Initiating therapy at diagnosis

<p style="text-align: center;">INSULIN THERAPY</p>	<p>o A home-based programme for initial management and education of children with diabetes and their families is an appropriate alternative to a hospital-based program.</p>
	<p>o Intensive insulin therapy should be delivered as part of a comprehensive support package.</p>
	<p>o The insulin regimen should be tailored to the individual child to achieve the best possible glycaemic control without disabling hypoglycaemia.</p>
	<p>o Medications other than insulin have no role in the management of type 1 diabetes.</p>
<p style="text-align: center;">DIETARY MANAGEMENT</p>	<p>o Dietary advice as part of a comprehensive management plan significantly improves glycaemic control.</p>
<p style="text-align: center;">PSYCHOLOGICAL INTERVENTIONS</p>	<p>o Psychological or educational interventions have positive effects on psychological outcomes, knowledge about diabetes and glycaemic control.</p>
	<p>o Encourage parental support and family communication, with targeted psychological treatment of family disruption and related stress factors.</p>
<p style="text-align: center;">LONG TERM COMPLICATIONS</p>	<p>□ Microvascular disease</p>
	<p>o To reduce the risk of long term microvascular complications, the target for all young people with diabetes is the optimising of glycaemic control towards a normal level.</p>
	<p>o From the age of 12 years, all people with diabetes should have the following annual checks:</p> <ul style="list-style-type: none"> - Examination of the retina - Measurement of microalbuminuria - Measurement of blood pressure
	<p>o There is no evidence that routine screening for autonomic neuropathy or hyperlipidaemia are of benefit.</p>
	<p>□ Associated conditions</p>
<p>o Young people with diabetes should be screened for thyroid and coeliac disease at onset of diabetes and at intervals throughout their lives.</p>	

3. Lifestyle Management

- Modification of adverse lifestyle factors is an important aspect of the management of both type 1 and type 2 diabetes.
- In particular, appropriate management of risk factors such as smoking, physical inactivity and poor diet is important for the retardation of microvascular and macrovascular complications.

□ Exercise and physical activity

- Regular physical activity is associated with a reduced risk of development of type 2 diabetes.
- In diabetic people, physical activity or exercise (e.g., daily walking) should be performed at least every second or third day to maintain improvements in glycemic control.
- Patients with existing complications of diabetes should seek medical review before embarking on exercise programmes.
- Exercise with normal insulin dose and no additional carbohydrate significantly increase the risk of hypoglycemia during and after exercise. Furthermore, injection of insulin into exercising areas increases the absorption of insulin and the risk of hypoglycemia and should therefore be avoided.

□ Healthy eating

- Intensive therapy or contact in diabetes shows clinically beneficial effects on weight and glycemic control during the period of intervention. More education and contact appears to improve outcomes.
- Encourage overweight individuals and those at high risk of developing diabetes to reduce their risk of developing diabetes by lifestyle changes.

□ Smoking cessation

4. Management of diabetic nephropathy

Diabetic nephropathy

- The presence of a raised urinary albumin excretion rate (>300mg/day) with or without a raised serum creatinine level in a patient with co-existing diabetic retinopathy.
- This represents a more severe and established form of renal disease and is more strongly predictive of total mortality, cardiovascular mortality and morbidity, and end-stage renal failure than microalbuminuria.

□ Risk factors

- Hyperglycemia
- Raised blood pressure
- Baseline urinary albumin excretion
- Increasing age
- Duration of diabetes
- Presence of retinopathy
- Smoking
- Genetic factors
- Raised cholesterol
- Male sex
- Serum homocysteine levels

Microalbuminuria

- It is the earliest sign of diabetic nephropathy and predicts increased total mortality, cardiovascular mortality and morbidity, and end-stage renal failure.

□ Screening

- All patients with diabetes should have their urinary albumin concentration and serum creatinine measured at diagnosis and at regular intervals, usually annually.
- Urinary albumin concentration should be measured using a first morning urine sample.
- An abnormal result should be confirmed by a further sample without delay.


□ Prevention of diabetic nephropathy

- Good glycaemic control (HbA1c around 7%) in all patients with diabetes and tight blood pressure control (< 140/80 mm Hg) in patients with type 2 diabetes should be maintained to reduce the risk of developing diabetic nephropathy.
- Blood pressure target in patients with renal impairment or nephritic range proteinuria is ≤ 125/75 mmHg.

□ Treatment of diabetic nephropathy

- Tight blood pressure control.
- Patients with microalbuminuria or proteinuria should be treated by:
 - Angiotensin converting enzyme inhibitors (ACEi), or
 - Angiotensin receptor blocker (ARBs).
- Diabetic patients with proteinuria and a reduced GFR should reduce dietary protein intake to 0.6 - 0.8 g/kg/day.
- Patients should be referred to a renal clinic if serum creatinine exceeds 150 mmol/l.

5. Diabetic cardiovascular disease

Risk factors <ul style="list-style-type: none"> • Smoking • Hypertension • Hyperglycemia • Dyslipidemia 	<ul style="list-style-type: none"> • Morbidity and mortality from cardiovascular disease (CVD) are 2-5 times higher in people with diabetes than the general population. • Current assessment methods may underestimate risk in people with type 1 diabetes or type 2 diabetes with nephropathy. • Diabetic patients more often present with a painless (silent) MI. 							
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Antiplatelet therapy								

Management of established CVD	<table border="1"> <tr> <td data-bbox="887 1144 1465 1256"> <ul style="list-style-type: none"> • Thrombolysis should not be withheld due to concern about diabetic retinopathy. </td> </tr> <tr> <td data-bbox="887 1256 1465 1368"> <ul style="list-style-type: none"> • Primary angioplasty may be more effective than thrombolytic therapy in diabetic patients with acute MI. </td> </tr> <tr> <td data-bbox="887 1368 1465 1442"> <ul style="list-style-type: none"> • Diabetes is not a contraindication to use of β-blockers. </td> </tr> <tr> <td data-bbox="887 1442 1465 1637"> <ul style="list-style-type: none"> • Indications for coronary angiography in patients with diabetes are similar to the general population, recognizing the increased risk of mortality following CABG and angioplasty. </td> </tr> <tr> <td data-bbox="887 1637 1465 1964"> <ul style="list-style-type: none"> • Incidence of contrast nephropathy is very high in diabetics specially those with proteinuria and/or renal impairment. Every precautions should be taken with adequate hydration of the patient, use of least dose of dye, use of the non-ionic dyes, use of calcium channel blockers and acetylcysteine. </td> </tr> </table>	<ul style="list-style-type: none"> • Thrombolysis should not be withheld due to concern about diabetic retinopathy. 	<ul style="list-style-type: none"> • Primary angioplasty may be more effective than thrombolytic therapy in diabetic patients with acute MI. 	<ul style="list-style-type: none"> • Diabetes is not a contraindication to use of β-blockers. 	<ul style="list-style-type: none"> • Indications for coronary angiography in patients with diabetes are similar to the general population, recognizing the increased risk of mortality following CABG and angioplasty. 	<ul style="list-style-type: none"> • Incidence of contrast nephropathy is very high in diabetics specially those with proteinuria and/or renal impairment. Every precautions should be taken with adequate hydration of the patient, use of least dose of dye, use of the non-ionic dyes, use of calcium channel blockers and acetylcysteine.
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<ul style="list-style-type: none"> o Intensive insulin treatment 						
<ul style="list-style-type: none"> o Thrombolytic therapy 						
<ul style="list-style-type: none"> o Consider primary angioplasty 						
<ul style="list-style-type: none"> o Long term aspirin + clopidogrel (75 mg/day) 						
<ul style="list-style-type: none"> o β-blocker therapy 						
<ul style="list-style-type: none"> o ACE inhibitor (within 48 hours in patients with LVSD) 						
<ul style="list-style-type: none"> o Statin therapy if total cholesterol >5 mmol/l 						
<ul style="list-style-type: none"> o Diabetic patients undergoing angioplasty should be treated with stents where feasible, and receive adjunctive therapy with abciximab 						

6. Management of diabetic foot disease

<ul style="list-style-type: none"> • Diabetic foot problems are a common complication of diabetes. • The absence of reliable symptoms and high prevalence of asymptomatic disease make foot screening essential. • Risk factors for peripheral vascular disease include: Smoking, Hypertension, and hypercholesterolaemia. 	<ul style="list-style-type: none"> • Risk factors for foot ulceration include: <ul style="list-style-type: none"> - Peripheral vascular disease. - Peripheral neuropathy. - Previous amputation. - Previous ulceration. - The presence of callus. - Joint deformity. - Visual/mobility problems. - Male sex.
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□ Care management

<ul style="list-style-type: none"> o All people with diabetes should be screened for foot disease o Foot care education as part of a multidisciplinary approach 	<p>Multidisciplinary team e. g. diabetes physician and specialist nurse, podiatrist, orthtist, vascular and orthopedic surgeons.</p>
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Footwear and others

Plantar pressure using ordinary shoes similar to barefoot

<ul style="list-style-type: none"> o Advise patients with diabetic foot disease to wear high-quality, cushioned-soled trainers rather than ordinary shoes o Custom-built footwear or orthotic insoles should be used to reduce callus severity and ulcer recurrence 	<p>Total contact casting</p> <ul style="list-style-type: none"> o Patients with unilateral plantar ulcers should be treated using total contact casting to optimise the healing rate of ulcers
	<p>Arterial reconstruction</p> <ul style="list-style-type: none"> o All patients with tissue loss and arterial disease should be considered for arterial reconstruction

□ Treatment

Pharmacological Therapy

<ul style="list-style-type: none"> o Start treatment of an infected diabetic foot ulcer with a broad spectrum antibiotic regimen in conjunction with appropriate debridement o Modify subsequent antibiotic regimens to bacteriology and clinical response 	<p>Painful diabetic neuropathy</p> <ul style="list-style-type: none"> o Consider tricyclic antidepressants (TCAs) as first line therapy in painful neuropathy o Gabapentin is also effective and is associated with fewer side-effects than TCAs and older anticonvulsants o Consider topical capsaicin for relief of localised neuropathic pain
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Tissue replacement therapy

<ul style="list-style-type: none"> o Consider treatment of refractory diabetic ulcers using living human tissue replacement, provided the patient meets strict exclusion criteria on infection, circulation and ulcer size and depth 	<p>Charcot's foot</p> <ul style="list-style-type: none"> • Charcot's foot is a neuroarthropathic process with osteoporosis, fracture, acute inflammation and disorganisation of foot architecture o Diagnose Charcot's foot by clinical examination supported by thermography o Total contact casting and non-weight bearing are effective treatments for acute Charcot's foot
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7. Risk assessment (adapted from the Tayside Foot Risk Assessment Protocol)

Diabetic patients should be assessed annually by a diabetologist, GP, or chiropodist to look for presence of neuropathy, ischemia or deformity

Patients should be categorised according to the presence of the following symptoms/signs:

<p>Normal sensation AND</p> <ul style="list-style-type: none"> • Good pulses • No previous ulcer • No foot deformity • Normal vision 	<p>ANY OF</p> <ul style="list-style-type: none"> • Loss of sensation • Absent pulses (or previous vascular surgery) • Significant visual impairment • Physical disability (e.g. stroke, gross obesity) 	<p>ANY OF</p> <ul style="list-style-type: none"> • Previous ulcer due to neuropathy and/or ischemia • Absent pulses and neuropathy • Callus with risk factor (absent pulse, neuropathy, foot deformity) • Previous amputation 	<ul style="list-style-type: none"> • Active foot ulceration, painful neuropathy which is difficult to control.
Low Risk	Moderate Risk	High Risk	Active Foot Disease
<ul style="list-style-type: none"> • No specific regular chiropody input needed (except in exceptional circumstances) • Patients can undertake their own nail care after appropriate education • Annual foot check 	<ul style="list-style-type: none"> • Regular (4-12 weekly) general chiropody • For patients with visual impairment or physical disability, who would otherwise fit into the low risk category, input from trained Foot Care Assistants can be substituted. 	<ul style="list-style-type: none"> • Chiropodist with interest and expertise in diabetes either at diabetes unit or in community center • Chiropodist may want to consider orthotic referral 	<ul style="list-style-type: none"> • Suggest contact with local specialist diabetes team (hospital-based)

In addition, patients with any of the following signs of ischaemia or infection should be considered for emergency referral to the hospital surgical receiving service or diabetic foot clinic, where appropriate:

<p>Critical ischaemia</p> <ul style="list-style-type: none"> • Rest or night pain • Pale/mottled feet • Dependent rubor • Ischaemic ulceration • Gangrene 	<p>Severe infection</p> <ul style="list-style-type: none"> • Abscess • Cellulitis
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8. Prevention of visual impairment

- Up to 39% of people with type 2 diabetes have retinopathy at diagnosis, 4-8% being sight-threatening

o Patients with multiple risk factors should be considered at high risk of developing eye disease.

- Rapid improvement in glycaemic control can lead to short term worsening of diabetic eye disease

o Stabilise sight-threatening eye disease before achieving significant improvement in glycaemic control.

Risk Factors:

- Poor glycaemic control
- Raised blood pressure
- Increasing microaneurysms
- Duration of diabetes
- Microalbuminuria
- Proteinuria
- Raised triglycerides
- Lowered hematocrit
- Pregnancy

Screening

- o Systematic screening for retinal disease should be provided for all people with diabetes.
- o Screening should be performed at a site convenient to patients.

Type 2 diabetes	⇒	o Screen from diagnosis
Type 1 diabetes	⇒	o Screen from age 12 or onset of puberty (whichever is first)
Systematic screening	⇒	o Retinal photography or slit lamp biomicroscopy
Opportunistic screening	⇒	o Dilated direct ophthalmoscopy

Treatment

Sight-threatening retinopathy (Moderate proliferative or worse)	⇒	o Laser photocoagulation
Severe pre-proliferative Or mild proliferative retinopathy	⇒	o Close follow up or laser photocoagulation

o Use focal laser photocoagulation for focal CSMO but not for ischaemic maculopathy
o Treat diffuse maculopathy if concern that disease is progressing
o Consider early vitrectomy for patients with type 1 diabetes and persistent vitreous haemorrhage, also for fractional retinal detachment threatening the macula / severe fibrovascular proliferation.
o Consider vitrectomy in patients with diffuse diabetic macular oedema.
o Provide community support, low vision aids and training to patients with visual impairment.

• Cataracts are a more common cause of visual impairment than retinopathy in type 2 diabetes	o Cataract extraction is advised when sight-threatening retinopathy cannot be excluded.
	o Cataract extraction should not be delayed.

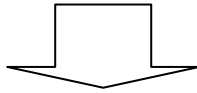
9. Diabetes in Pregnancy

Type 1 diabetes is a high risk state for the woman and her fetus due to increased risks of:

Complications of diabetes	Obstetric complications	Fetal & neonatal complications
<ul style="list-style-type: none"> • Ketoacidosis • Severe hypoglycemia • Progression of microvascular complications 	<ul style="list-style-type: none"> • Pre-eclampsia • Maternal infection • Polyhydramnios • Premature labour • Obstructed labour 	<ul style="list-style-type: none"> • Fetal distress • Late intrauterine death • Congenital malformation • Respiratory distress syndrome • Jaundice

Pre-pregnancy care

- o Pregnancy should be planned, with good contraceptive advice and pre-pregnancy care.
- o Pre-pregnancy care should be provided by a multidisciplinary team.



- Review of medical, obstetric and gynaecological history
- Advice on glycaemic control
- Screening for complications

Delivery

- o Uncomplicated pregnant diabetic women should be assessed at 38 weeks to ensure delivery by 40 weeks.
- o Delivery in consultant-led maternity units with senior physician, obstetrician and neonatologist available.
- o Monitor progress of labour as for other high risk women, including continuous electronic fetal monitoring.
- o IV insulin and glucose as necessary to keep blood glucose 4-7 mmol/l.

Infants of mothers with diabetes

- o Early feeding is advised to avoid neonatal hypoglycaemia and to stimulate lactation.
- o Breastfeeding is recommended, but support mothers in their method of choice.

Nutritional management

- o Before and during pregnancy, aim for blood sugar between 4 and 7 mmol/l
- o Dietetic advice should be available in all diabetic antenatal clinics.
- o Encourage diet including high complex carbohydrates, soluble fibre and vitamins, reduced saturated fats.
- o Pre-pregnancy folic acid supplements (0.4 mg) to continue up to 12 weeks gestation.

Complications during pregnancy

OBSTETRIC COMPLICATIONS:

- Manage as for all pregnant women

METABOLIC COMPLICATIONS:

- Explicit local emergency contact arrangements

MICROVASCULAR COMPLICATIONS:

- o Fundal examination each trimester.
- o Early referral of women with moderate retinopathy to an ophthalmologist.
- o As renal section but avoid ACE inhibitors.
- o Suitable antihypertensive agents include methyldopa, labetalol and nifedipine.

Gestational diabetes

- o Women with GDM should receive intensive management with diet and/or insulin if macrosomia is suspected or if blood glucose levels are in the range for established diabetes.

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