Type 2 diabetes: an epidemic in the making

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For editorial comment, see "Screening out diabetes" on page 34.

Abstract

- It is estimated that more than 1.2 million adult Australians will have diabetes by the end of the decade, with only half of those affected being aware of their condition.
- Type 2 diabetes mellitus (T2DM) is characterised primarily by insulin resistance, in which increased insulin is required to produce a normal blood glucose level. Individuals with prediabetes or T2DM are at increased risk of cardiovascular disease and usually have what is called the metabolic syndrome.
- All patients aged 55 years and over should be screened for diabetes, as should younger people who have particular risk factors such as obesity, family history, hypertension or belonging to a high risk ethnic group. Screening should be performed first with a test of fasting plasma glucose level (FPG), with the oral glucose tolerance test being performed only when the FPG test is equivocal.
- Initial management of T2DM targets insulin resistance by lifestyle modification (weight loss and exercise) and pharmacological therapies (metformin and thiazolidenediones). Medications which increase pancreatic insulin secretion (sulfonylureas) are also often required. Most patients require multiple oral agents to achieve recommended glycaemic targets.
- Insulin therapy becomes necessary when glycaemic targets are not reached despite treatment. When explaining why insulin has become necessary, it is important to remind patients of the natural history of T2DM and the benefits of better glycaemic control.
- Therapy for T2DM should be monitored by capillary blood glucose monitoring by the patient and by periodic testing of HbA_{1c} levels. The HbA_{1c} target may need to be individualised for each patient, but the goal should be an HbA_{1c} level of 7%.
- It is important not to treat the blood glucose level only, but also to recognise and treat hypertension, dyslipidaemia, smoking and obesity to reduce morbidity and mortality from microvascular and cardiovascular disease.

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DIABETES MELLITUS is a syndrome of abnormal glucose metabolism characterised by hyperglycaemia. It is associated with insulin deficiency — a relative or absolute impairment in pancreatic insulin secretion, along with varying degrees of peripheral resistance to the action of insulin. Type 1 diabetes mellitus (T1DM) is characterised by destruction of the pancreatic beta islet cells resulting in an absolute deficiency of insulin. This is usually due to autoimmune damage to the pancreas. Type 2 diabetes mellitus (T2DM) is a different disorder, characterised primarily by insulin resistance in muscle, liver and fat. This is associated with inability of the pancreas to secrete enough insulin to overcome the defect. T2DM is by far more common, comprising more than 95% of cases of diabetes worldwide. T2DM is the focus of this review.

T2DM has become epidemic in the past few decades, with a dramatic increase in its incidence worldwide. In Australia, the AusDiab study reported that in 2000 7.4% of the population aged 25 or over had diabetes.[1] This study also found that for every diagnosed case of diabetes there is an undiagnosed case. As it is often asymptomatic in its early stages, T2DM can remain undiagnosed for many years. The prevalence of T2DM has doubled in the last 20 years and it is estimated that more than 1.2 million Australians 25 years and over will have diabetes by 2010.[1]

Insulin resistance and the metabolic syndrome

Insulin resistance is a condition in which increased insulin is required to produce a normal biological response (ie, a normal blood glucose level). Insulin resistance is caused by both acquired (weight gain, reduced

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exercise) and genetic factors. It is often accompanied from early on in the disease process by other cardiovascular risk factors, including increased abdominal fat, hypertension, elevated glucose levels and dyslipidaemia — a constellation of features known as the metabolic syndrome. Significantly, the metabolic syndrome markedly increases the risk for the development of cardiovascular disease in individuals whether or not they have developed diabetes.[2,3]

While insulin resistance exists in virtually all individuals with T2DM, it is frequently present in the metabolic syndrome (which often precedes the onset of T2DM) even in the absence of hyperglycaemia. In those patients with insulin resistance who have normal blood glucose levels, fasting insulin levels are elevated. However, routine measurement of fasting insulin levels is of little value as a clinical test.

Criteria have been established for the diagnosis of the metabolic syndrome. Currently, the National Cholesterol Educational Program (NCEP) Adult Treatment Panel III (ATP III) guidelines are most commonly used.[4] Other criteria, such as those of the World Health Organization (WHO), are also used.[5] The guidelines from the NCEP ATP III suggest that the clinical diagnosis of the metabolic syndrome should be made in the presence of any 3 of the following:

- Abdominal obesity, defined as a waist circumference in men > 102 cm and in women > 88 cm
- High triglycerides (≥ 1.7 mmol/L)
- Low high-density-lipoprotein (HDL) cholesterol (< 1 mmol/L in men and < 1.3 mmol/L in women)
- Elevated blood pressure (≥ 130/≥ 85 mmHg or current antihypertensive therapy)
- Fasting plasma glucose ≥ 6.1 mmol/L

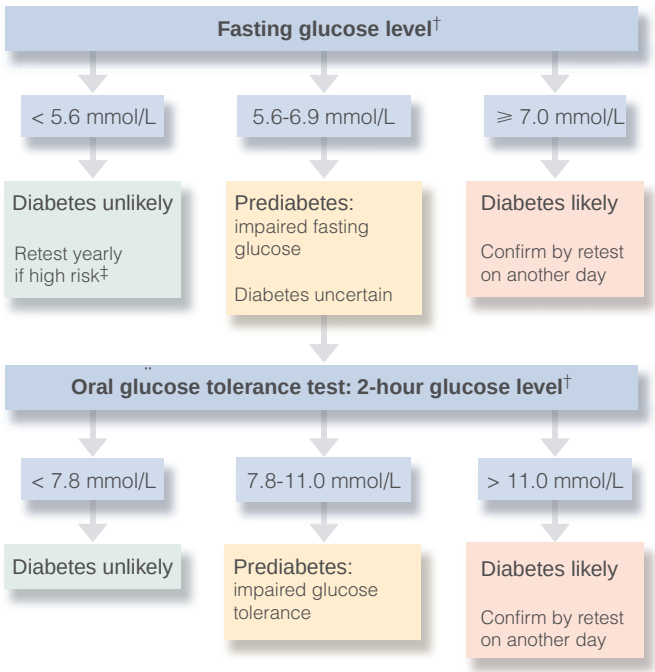
The WHO definition is based on the presence of T2DM or impaired glucose tolerance (IGT) plus the presence of any two of the above abnormalities including microalbuminuria.

Prediabetes

Before developing overt T2DM, patients hypersecrete insulin to maintain normal blood glucose levels. Eventually the ability of pancreatic beta-cells to secrete insulin becomes impaired in the face of continued insulin resistance. Blood glucose levels then begin to rise and the patient develops prediabetes. Prediabetes is a new term intended to replace the previously used "impaired glucose tolerance" (IGT) and "impaired fasting glucose" (IFG). These terms are descriptive and helpful, but can be confusing for patients and doctors. Prediabetes is defined as a fasting plasma glucose level in the range 5.6–6.9 mmol/L (IFG), or a 2-hour plasma glucose level (after a 75 g oral glucose load) of 7.8–11.0 mmol/L (IGT). More than 2 million Australians aged 25 years and over are affected.[1]

An international expert committee on the diagnosis and classification of diabetes mellitus recently revised criteria for the diagnosis of IFG.[6] On the basis of epidemiological predictive data, it lowered the bottom of the cut off for IFG from 6.1 mmol/L to 5.6 mmol/L. This optimises the sensitivity and specificity for predicting future diabetes and increases the frequency of diagnosis of prediabetes by about 20%.

Diagnosis of prediabetes and type 2 diabetes mellitus*



* Adapted from Holmwood C, Phillips P, Harris P, et al. Diabetes management in general practice. 8th ed. Canberra: Diabetes Australia, 2002.
†Glucose levels measured in venous plasma.
‡High risk: See "Who should be screened for undiagnosed diabetes?"

Prediabetes is accompanied by an increased risk of both cardiovascular disease and T2DM. Patients with IGT have a stronger association with cardiovascular disease risk factors, cardiovascular disease events and mortality[7,8] compared with IFG (which in itself implies a higher cardiovascular disease risk than normal blood glucose levels). However, both IGT and IFG are similarly associated with an increased risk of diabetes, estimated at 10% progression each year from prediabetes to diabetes. The risk is higher if the prediabetic patient has both IGT and IFG.

Patients identified as having prediabetes should have a review of lifestyle and cardiovascular disease risk factors. Intervention is recommended to reduce further problems. We now know from studies such as the Diabetes Prevention Program (DPP)[9] and the Finnish Diabetes Study[10] that we can prevent or substantially delay the progression from IGT to T2DM through intensive lifestyle treatment, such as exercise and diet therapy. Early diagnosis of prediabetes and intervention could also prevent diabetic complications. At present there are numerous people in the community who have diabetes but remain undiagnosed for many years. Complications are usually present at diagnosis of diabetes (microvascular diabetic complications are present in up to 20% of patients when first diagnosed with T2DM). Lifestyle interventions are likely to reduce cardiovascular disease and total mortality, while drugs which reduce insulin resistance, such as metformin or the thiazolidenediones, may help. Further studies are required to elucidate these issues.

Diagnosis

T2DM is diagnosed when the fasting plasma glucose level (FPG) is ⩾ 7.0 mmol/L or when the plasma glucose level 2 hours after a 75 g oral glucose-tolerance test (OGTT) is > 11.0 mmol/L. Fasting is defined as no consumption of food or beverage other than water for at least 8 hours before testing. In asymptomatic patients, the FPG and results of the OGTT should be confirmed by retesting on another day. In the presence of symptoms due to hyperglycaemia, a diagnosis of diabetes can be made with just one abnormal test or if a random plasma glucose level is above 11.0 mmol/L — a reading at any time of the day regardless of the time of the last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

In the past there has been disagreement as to whether the FPG or the OGTT should be the initial screening test used for diagnosis of diabetes. The American Diabetes Association (ADA) expert committee has recommended that the FPG should be the diagnostic test of choice, both for clinical and epidemiological purposes. However, the World Health Organization (WHO) has recommended the use of the OGTT in some circumstances. The OGTT needs to be carried out after an overnight fast following three days of adequate carbohydrate intake (greater than 200 g per day). The OGTT better identifies high-risk subjects for diabetes and cardiovascular disease (ie, those with IGT) and also those diabetic patients with a normal FPG but elevated 2-hour plasma glucose levels (as occurs in some ethnic groups; eg, Chinese). However, the OGTT is more costly, inconvenient and time-consuming than the FPG, and the repeat test reproducibility is worse.[11,12]

The OGTT is not recommended as the first step in screening (ADA and WHO) but rather as a confirmation test. The FPG should be the first screening test, and if the FPG level is 5.5–6.9 mmol/L the patient should be followed up with an OGTT (Box). If the 2-hour plasma glucose level is < 7.8 mmol/L, the patient does not have diabetes. Patients at increased risk of developing diabetes should be retested every 3 years, or annually if they are at high risk. The same management plan applies if the patient is diagnosed with IGT (2-hour plasma glucose of 7.8–11.0 mmol/L). When following up these patients, the FPG should be the first test used, as it will avoid the more time consuming OGTT should the patient's FPG level be diagnostic for diabetes. The OGTT will only have a role in these circumstances if the FPG test is equivocal (FPG 5.5–6.9 mmol/L).

The HbA_{1c} test — an index of average blood glucose levels during the previous three months — remains a valuable tool to monitor glycaemia and an indicator of therapeutic response, but it is not recommended for the screening or diagnosis of diabetes because of the lack of local and international laboratory standardisation of reference ranges and the confounding effect of other conditions (such as pregnancy, uraemia, haemoglobinopathies, blood transfusion and anaemia). Capillary blood glucose testing using a blood glucose meter is too imprecise for diagnosis and should only be used for self-monitoring.

Who should be screened for undiagnosed diabetes?

All patients aged 55 years and over should be screened for diabetes. Testing should be performed at age 45 and over if a person is obese (body mass index > 30), has a first degree relative with T2DM, or has hypertension. Certain ethnic groups (Pacific Islanders, Indians, Chinese and Aboriginal and Torres Strait Islanders) should be tested at age 35 and over, because of the high incidence of T2DM in these groups. All people with prediabetes or clinical cardiovascular disease (myocardial infarction, angina or stroke) and women with the polycystic ovary syndrome or a previous history of gestational diabetes are at high risk and should be screened, regardless of age.

When both tests are performed, a result indicative of diabetes for either one is diagnostic (subject to confirmation by retesting on another day).

Management

The major aim of diabetes management is to prevent diabetes-related complications, both microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (stroke, ischaemic heart disease, peripheral vascular disease). Aggressive, tight control of blood glucose reduces morbidity from diabetes. The United Kingdom Prospective Diabetes Study, the largest and longest prospective randomised trial in people with T2DM, showed that a reduction in HbA_{1c} by just 1 percentage point reduced the risk of microvascular disease by an average of 37%.[13] T2DM is usually part of the metabolic syndrome, so it is important to treat comorbidities in patients with T2DM, particularly hypertension, dyslipidaemia, smoking and obesity. The United Kingdom Prospective Diabetes Study demonstrated that aggressive control of blood pressure lowered the incidence of diabetic complications by 24%.[14] This was true for both microvascular and macrovascular disease and was even more marked than the effect of intensive blood glucose control. The importance and effectiveness of the multifactorial approach in treating T2DM was studied recently with a stepwise implementation of behaviour modification and drug therapy that targeted hyperglycaemia, hypertension, dyslipidaemia, and microalbuminuria.[15] The study suggested that the greatest benefits in preventing cardiovascular disease are seen when glucose, blood pressure and lipid levels are targeted simultaneously.

Targeting insulin resistance

The initial management of T2DM targets insulin resistance, the underlying pathogenetic factor causing the metabolic disturbance. This can be achieved by lifestyle modification (weight loss and exercise). Pharmacological therapies specifically aimed at reducing insulin resistance (metformin and thiazolidenediones) may help. Realistic targets should be set regarding weight loss, keeping in mind that a 5 kg weight loss can reduce insulin resistance by 25%–50%[16] as well as improving blood pressure and lipid levels. Patients should be advised on nutrition therapy by a dietitian. Exercise should take the form of a regular

brisk walk for 30 minutes, 5 times a week. Patients with previously sedentary lifestyles should start with a shorter duration of low- to moderate-intensity activity, gradually increasing to the set goal. The exercise prescription may need to take the form of non-weight bearing exercise such as swimming or resistive exercises with free-weights in people with chronic disability who are unable to bear weight for long periods.

In patients who are unable to adopt the necessary lifestyle modifications, or who do so but show signs of worsening glycaemia, an oral antihyperglycaemic agent should be prescribed. Metformin is almost always the primary drug of choice in T2DM as it improves glucose tolerance by enhancing insulin sensitivity. It also has the advantage of improving glycaemic control without the risk of weight gain and hypoglycaemia. The United Kingdom Prospective Diabetes Study showed that metformin was the only therapy during intensive control of hyperglycaemia that reduced the risk of myocardial infarction in subgroup analysis of obese patients with T2DM.[17] Gastrointestinal complaints may occur in some patients with metformin therapy, but are minimised if patients are started on a low dose that is titrated slowly to a maximum of 3 g daily.

The thiazolidinediones (rosiglitazone and pioglitazone) are another class of oral antihyperglycaemic agents which reduce insulin resistance via a different mechanism from metformin. Their hypoglycaemic effect may not be seen for 4 to 6 weeks and is similar (in terms of HbA_{1c} reduction) to metformin and other oral antihyperglycaemic agents, but may be longer lasting. Considerable data have accumulated recently to show that thiazolidinediones may have beneficial effects on the atherogenic process within the vessel wall,[18] as well as reducing blood pressure and producing a less atherogenic lipid profile. These effects make them excellent choices in treating patients with the metabolic syndrome (most T2DM patients). Whether the beneficial effects on surrogate markers for cardiovascular disease translate into a reduction in cardiovascular disease events is yet to be shown in clinical studies. The beneficial effects of thiazolidinediones are additive to those of metformin.

Adverse effects of thiazolidinediones include weight gain and fluid retention. Liver function tests should be monitored periodically during treatment. Thiazolidinediones have only recently been listed on the Pharmaceutical Benefits Scheme, and their use in Australia will be restricted to prescribing them in combination with either metformin or sulfonylureas for patients in whom combination therapy with metformin plus sulfonylureas is contraindicated or not tolerated. Pioglitazone is the only thiazolidinedione which has an indication for use in combination with insulin in T2DM. Unlike metformin, these agents are safe for patients with a high creatinine level and are an alternative to metformin as first line therapy in patients who cannot tolerate the gastrointestinal side effects of metformin.

Stimulating insulin secretion

Results of the United Kingdom Prospective Diabetes Study showed that most patients with T2DM required treatment with multiple oral antihyperglycaemic agents to achieve recommended glycaemic targets. After insulin resistance has been reduced, the next step is to use medications which increase pancreatic insulin secretion. The insulin secretagogues include the sulfonylureas and the newer meglitinides (not available on the Pharmaceutical Benefits Scheme). Sulfonylureas are the secretagogues of choice; they are usually added to existing therapy directed towards reducing insulin resistance. Second-generation sulfonylureas (gliclazide, glipizide, glimepiride and glibenclamide) have structural characteristics that allow them to be given in much lower doses than their predecessors. The several sulfonylureas vary in their metabolism and biological effects. Glibenclamide has a very long half-life, owing to formation of active metabolites that are usually excreted by the kidney, and so should not be used in patients with renal impairment or the elderly due to the risk of protracted severe hypoglycaemia. The sulfonylureas have roughly the same effect on lowering HbA_{1c} as other oral antihyperglycaemic agents (about 1.5 percentage points), but usually lose their effectiveness over time due to the natural history of progressive insulin deficiency in T2DM. This natural history is not affected by pharmacological treatment.

The meglitinides (nateglinide and repaglinide) are relatively short-acting agents that increase pancreatic insulin secretion. Their main use is in reducing postprandial hyperglycaemia, and they should be administered immediately before meals. They should be considered in patients with irregular meal patterns.

The only other class of oral antihyperglycaemic agents are the alpha-glucosidase inhibitors (acarbose). They work by delaying intestinal carbohydrate absorption by competitively inhibiting the enzyme responsible for breakdown of disaccharides and complex polysaccharides. Acarbose has a supportive role in treating T2DM and is usually only used in combination with metformin and/or a sulfonylurea. It is the least potent of the oral antihyperglycaemic agents, with no more than a 1 percentage point reduction in HbA_{1c} likely to be achieved by addition of this drug. Acarbose occasionally has a role in patients who are just above the target HbA_{1c} level when treated with maximal doses of metformin and a sulfonylurea. An unfortunate side effect of acarbose is the high incidence of gastrointestinal symptoms and bloating. These symptoms have limited its clinical use.

Use of insulin in T2DM

Pancreatic function, and therefore insulin secretion, progressively declines in T2DM. We know from the United Kingdom Prospective Diabetes Study that patients with T2DM have less than 25% of normal insulin secretion 6 years after diagnosis.[13] This is why oral antihyperglycaemic agents eventually lose effect in almost all T2DM patients. Secondary treatment failure is defined clinically when blood glucose levels deteriorate after an initially good response to oral antihyperglycaemic agents. The patient is usually on maximal doses of more than one oral antihyperglycaemic agent with a suboptimal HbA_{1c} level. This situation requires insulin treatment in T2DM. It is important to note that the patient now has insulin-requiring T2DM. This is a different condition to T1DM or the previously used description, insulin-dependent diabetes mellitus.

Before starting insulin treatment in T2DM, it is important to make sure the patient has been compliant with their prescribed oral antihyperglycaemic agent therapy and that secondary causes of hyperglycaemia are not present. (Infection, occult malignancy, hyperthyroidism and drugs such as corticosteroids all worsen glycaemia.) Patients are often reluctant to commence insulin treatment for several reasons, including fear of using an injectable drug and risk of hypoglycaemia and weight gain. However, it is important to remind patients of the natural history of T2DM when explaining why insulin has become necessary. As well, mention should be made of the benefits of better glycaemic control: reducing the risk of microvascular complications and improving well being.

It is important not to delay the introduction of insulin treatment in patients with secondary treatment failure. During titration of the insulin regimen, patients may be reluctant to accept higher insulin dosages. Insulin has no upper dose limit, and it is the target HbA_{1c} level which is important, not the actual dose required to achieve that level of control. The risk of severe hypoglycaemia is not as common as in T1DM. Nevertheless, nocturnal hypoglycaemia is possible and should be avoided as far as possible, as it constitutes a significant risk in elderly patients, especially those who live alone.

The patient with insulin-requiring T2DM starts with a once daily long-acting insulin (eg, Protaphane) injection at bedtime. This controls overnight liver glucose output and the fasting glucose level. At this stage, the patient should continue taking oral antihyperglycaemic agents. There is extensive evidence that insulin is effective when administered in combination with any of the oral antihyperglycaemic agents. The most effective combination seems to be insulin with metformin, particularly in terms of weight gain, glycaemic control and reducing insulin requirements.[19] If glycaemic control remains suboptimal, the regimen will need to be changed to twice daily insulin injections of either a long-acting or a pre-mixed insulin preparation (containing fixed proportions of short-acting and long-acting insulin, e.g. Mixtard 30/70 and Novomix 30).

The newer insulin-analogue preparations have allowed more physiological insulin to be used. Very short-acting (insulin-aspart and insulin-lispro) and long-acting (glargine, detemir) insulin-analogue preparations have been developed as well as mixtures. The long-acting insulin analogue preparations are not currently available on the Pharmaceutical Benefits Scheme. The newer agents have allowed insulin-requiring patients to achieve good glycaemic control with fewer episodes of hypoglycaemia. Nocturnal hypoglycemia is less frequent with the long-acting analogues.

Monitoring therapy and glucose control

Therapy for T2DM should be monitored by capillary blood glucose monitoring by the patient and by periodic testing of HbA_{1c} levels. The serial HbA_{1c} level is the best correlate of microvascular complications, while home blood glucose monitoring helps the stabilisation and education process. It also alerts patients to sudden or gradual deterioration in glycaemic control and in their recognition of hypoglycaemia.

The HbA_{1c} target may be individualised for each patient, but the usual goal should be a level of 7%. An HbA_{1c} of 6.5% is the preferred target for younger patients with T2DM, also for those with early microvascular complications and patients with a family history of diabetic nephropathy. In older patients, particularly the more frail elderly patient, the goal is not so much the HbA_{1c} level but rather avoiding symptomatic hyperglycaemia and hypoglycaemia.[20]

Just as important as glycaemic control in the management of T2DM is the detection of comorbidities, followed by aggressive treatment to achieve recommended targets. Besides an HbA_{1c} level of less than 7%, treatment to target levels of blood pressure (< 130/80 mmHg) and blood lipid profile (low-density-lipoprotein cholesterol < 2.5 mmol/L) is essential. Cardiovascular disease prevention with regular low-dose aspirin, cessation of smoking and restoration of ideal body weight are all needed to help reduce morbidity and mortality from microvascular and cardiovascular disease.

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