Does your patient have glucose intolerance?

Persons with impaired glucose tolerance are at very high risk of developing type 2 diabetes. Several recent successful interventional studies targeting subjects with impaired glucose tolerance have stimulated enthusiasm for prevention of type 2 diabetes.

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Type 2 diabetes is positioned to be one of the largest epidemics in human history, and it is one of the major threats to human health in the 21st century.[1] The past two decades have seen an explosive increase in the number of people with diabetes globally. It is estimated that the total number of people with diabetes worldwide will rise from 194 million in 2003 to 333 million by 2025.[2] The number of people with diabetes is predicted to increase in virtually every nation in the world, with the greatest increases expected in developing countries and the socially disadvantaged groups in developed nations. In the Australian Diabetes, Obesity and Lifestyle Study (AusDiab), the prevalence of impaired glucose tolerance in adults was 10.6%; this translates to almost 1,300,000 people.[3]

A number of small studies have demonstrated the benefits of lifestyle interventions in delaying progression from impaired glucose tolerance (IGT), a high risk category, to type 2 diabetes. Two recent successful intervention studies targeting subjects with IGT – the Finnish Diabetes Prevention Study and the US Diabetes Prevention Program – have stimulated enthusiasm for efforts to prevent type 2 diabetes.[4,5] In these studies, lifestyle interventions targeted at overweight people with IGT reduced the risk of progression to diabetes by more than 50%. The studies confirm the strategies used in the first major lifestyle intervention, the Da Qing study in China.[1]

What is impaired glucose tolerance?

IGT is defined as a condition in which blood glucose levels are higher than normal but not high

IN SUMMARY

- **In the Australian Diabetes, Obesity and Lifestyle Study (AusDiab), the prevalence of impaired glucose tolerance (IGT) in adults was 10.6%. This translates to almost 1,300,000 people.**
- **If the fasting plasma glucose is between 5.5 and 6.9 mmol/L, or the random blood glucose is between 5.5 and 11.0 mmol/L, an oral glucose tolerance test is recommended.**
- **Detection of IGT, an asymptomatic condition, is unlikely to provide optimal benefit unless it is accompanied by a comprehensive health assessment that includes consideration of obesity, blood pressure and serum lipids.**
- **People with IGT are at very high risk of developing type 2 diabetes, and lifestyle intervention studies into preventing diabetes have targeted these people.**
- **The principles of successful lifestyle interventions for diabetes prevention are weight loss, regular physical activity and a fibre-rich diet tin which less than 30% of total energy is fat and less than 10% of total energy is saturated fat.**
- **The use of pharmacological agents for type 2 diabetes prevention is being explored.**
- **Longer-term follow up studies are needed to establish whether lifestyle and pharmacological interventions actually prevent type 2 diabetes or merely delay its onset.**

Table 1. Diagnostic criteria for categories of glycaemia

No diabetes
Fasting plasma glucose < 6.1 mmol/L and
2h plasma glucose* < 7.8 mmol/L (if measured)†

Impaired fasting glucose
Fasting plasma glucose 6.1 to 6.9 mmol/L and
2h plasma glucose < 7.8 mmol/L

Impaired glucose tolerance
Fasting plasma glucose < 7.0 mmol/L and
2h plasma glucose 7.8 to 11.0 mmol/L

Diabetes
Fasting plasma glucose ≥ 7.0 mmol/L and/or
2h plasma glucose ≥ 11.0 mmol/L (if measured)

* 2h plasma glucose values measured after an oral glucose tolerance test (OGTT) with 75 g anhydrous glucose.
† OGTT not recommended for fasting plasma glucose values outside the range 5.5 to 6.9 mmol/L.

enough to be classified as diabetes (Table 1). Apart from their high risk of type 2 diabetes, people with IGT also have a heightened risk of macrovascular disease because of the association with other known cardiovascular risk factors, including hypertension, dyslipidaemia and central obesity.[6] Therefore, a diagnosis of IGT, particularly in apparently healthy and ambulatory individuals, has important prognostic implications.

IGT is a stage in the natural history of disordered carbohydrate metabolism. A stage called 'impaired fasting glycaemia' (IFG) was introduced by the World Health Organization in 1999, referring to fasting glucose concentrations that are lower than those required to diagnose diabetes but higher than the normal reference range (Table 1).[7] IGT and IFG are not clinical entities in their own right but are risk categories for future diabetes and cardiovascular disease. They represent impaired glucose regulation, and refer to a metabolic state intermediate between normal glucose homeostasis and diabetes. Both IGT and IFG are often associated with other components of the metabolic syndrome.[1,6] IFG will not be discussed in detail in this article.

An individual with a fasting plasma glucose concentration between 6.1 mmol/L and 6.9 mmol/L is considered to have IFG (Table 1). If an oral glucose tolerance test (OGTT; 75 g anhydrous glucose) is performed, the diagnostic cut-points for IGT are fasting glucose less than 7 mmol/L and 2-hour post oral glucose between 7.8 and 11.1 mmol/L.

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Figure 1. Laboratory fasting plasma glucose is a recommended screening test for type 2 diabetes.

IGT screening and diagnosis

Evidence-based guidelines endorsed by the National Health and Medical Research Council (NHMRC) helpoptimise case finding of patients with undiagnosed diabetes in primary care in Australia.[8] These advocate testing for undiagnosed type 2 diabetes in certain high risk groups (see Table 2), and recommend laboratory plasma glucose (preferably fasting) as a screening test (Figure 1). Although the OGTT has the disadvantage that it is labour-intensive and cumbersome for patients and there are concerns about its reproducibility, its use is recommended in Australia in people with blood glucose values in the uncertain range.

According to the guidelines, if the fasting glucose is less than 5.5 mmol/L, then diabetes is unlikely. A fasting glucose of 7.0 mmol/L or more, or a non-fasting glucose of 11.1 mmol/L or more, makes diabetes likely and the diagnosis is confirmed by a repeat abnormal test. If the fasting glucose is between 5.5 and 6.9 mmol/L, or the non-fasting glucose is between 5.5 and 11.0 mmol/L, an OGTT with 75 g anhydrous

glucose is recommended. This strategy was designed for the identification of people with undiagnosed diabetes, rather than IGT. However, the risk factors are essentially the same.

A cut-off fasting glucose of 5.5 mmol/L for performing the OGTT will result in missing up to 50% of people with IGT. More people would be diagnosed using a lower cut-off fasting glucose, but those group that is missed using the cut-off of 5.5 mmol/L are at a lower risk of developing diabetes than those identified,[5] and the missed cases should be picked up with repeat screening in subsequent years before diabetes develops.

Blood glucose testing, therefore, is required only in people with risk factors, and ideally begins with a fasting glucose and progresses to an OGTT where necessary (Table 3).

The purpose of diagnosing IGT is to initiate treatment (lifestyle modification or drug therapy) that will reduce the risk of progression to diabetes, and possibly cardiovascular disease. Detection of IGT, an asymptomatic condition, is unlikely to provide optimal benefit unless other lifestyle-related conditions requiring treatment are also considered. This includes assessment of obesity, blood pressure, serum lipids and physical activity.

IGT and the metabolic syndrome

IGT is often a manifestation of a much broader underlying disorder. The metabolic syndrome (sometimes called syndrome X) is a cluster of cardiovascular risk factors that includes, apart from glucose intolerance (IGT or diabetes), hyperinsulinaemia, dyslipidaemia, hypertension, visceral obesity, hypercoagulability and microalbuminuria (Figure 2). This association also influences contemporary management of IGT. Evidence now exists for a far more aggressive approach to not just the prevention of diabetes but also the treating of other cardiovascular risk factors.

Preventing type 2 diabetes – the reality and the challenge

It does not come as a surprise, given the dramatic increase in type 2 diabetes and its complications and socioeconomic impact, that there is now great interest in primary prevention. People with IGT are at the top of the list of targeted people. Several studies have clearly shown that lifestyle modification (such as weight reduction and increased physical activity) can dramatically reduce the incidence of type 2 diabetes in high risk subjects.[1,4,5] Lifestyle intervention studies have shown that quite modest changes can reduce the progression from IGT to diabetes by 50 to 55%.[4,5]

The principles of the successful lifestyle interventions for diabetes prevention are:

- 5 to 7% weight loss
- moderate intensity physical activity of at least 150 minutes per week
- total fat intake less than 30% of total energy intake
- saturated fat intake less than 10% of total energy intake
- fibre intake more than 15 g per 1000 kcal (4190 J).

An important issue is whether the

Table 2. Type 2 diabetes screening: NHMRC recommendations[8]

- People aged 55 years and over
- People age 45 years and over who have at least one of the following:
  - obesity (BMI ≥ 30 kg/m^2)
  - a first degree relative with diabetes
  - hypertension
- People aged 35 years and over with one of the following ethnicities:
  - Aboriginal or Torres Strait Islander
  - Pacific Islander
  - are from the Indian subcontinent
  - Asian
- People with a history of cardiovascular disease
- People with impaired glucose tolerance or impaired fasting glucose
- Women with a history of gestational diabetes
- Women with polycystic ovary syndrome who are obese

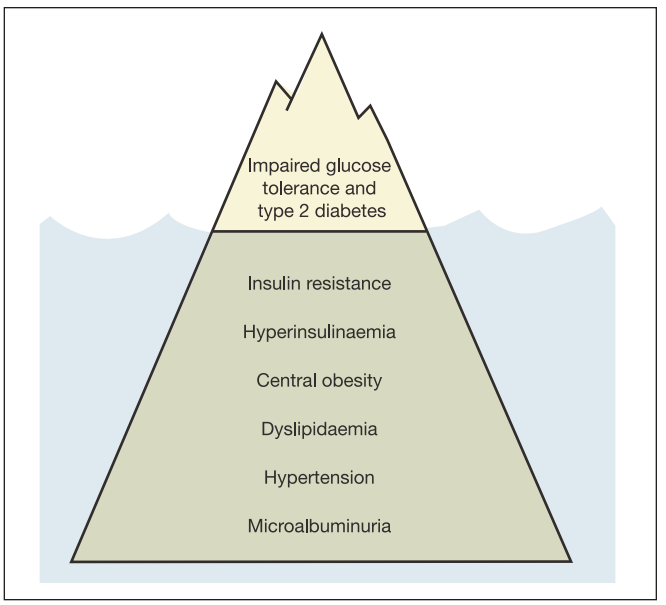

Figure 2. The metabolic syndrome is synonymous to an iceberg with glucose intolerance above the surface but a group of other key cardiovascular risk factors lurking below.

Table 3. Diabetes testing strategy

1. Assess individual for risk factors for undiagnosed diabetes (see Table 2)
2. Measure fasting plasma glucose in those with risk factors
3. Further testing with OGTT depending on result of fasting plasma glucose

findings of the two major studies in developed countries, the Finnish Diabetes Prevention Study and the Diabetes Prevention Program, can be applied to individual patients. Underpinning the enthusiasm for lifestyle and behavioural modification – clearly the first strategy – there needs to be a realistic approach to interventions with a good understanding of the socioeconomic, cultural and demographic issues and perceptions surrounding chronic diseases such as diabetes. In practice, it is likely that a number of strategies will be needed to complement the lifestyle approach.

The general practitioner needs to assess each person with diabetes not only for glycaemic status but also for other cardiovascular risk factors. Lifestyle advice specific for each person should be provided. People with IGT require follow up, and should be retested annually for progression to diabetes.

The use of pharmacological agents for type 2 diabetes prevention is also being explored and, while contrary to an appropriate community-based or individual lifestyle intervention strategy, drugs already used in the management of diabetes may be considered where lifestyle intervention fails or is difficult from a sociocultural perspective.

Benefits, in terms of diabetes prevention, have been found using metformin, acarbose and the thiazolidedione troglitazone (withdrawn from the market because of adverse hepatic effects).[9] Large intervention studies are currently in progress with ramipril and rosiglitazone (the DREAM [Diabetes REduction Approaches with ramipril and rosiglitazone medications] study), and with valsartan and nateglinide (the NAVIGATOR [Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research] study). It is unlikely that pharmacological intervention will be recommended for large scale use in IGT until it can be shown that it not only prevents the development of diabetes but also clinical cardiovascular disease.

Conclusion

Although preventive action – lifestyle or pharmacological – will not be easy or cheap, the magnitude of the problem we face with diabetes and its complications demands serious action. Intervention with drugs poses issues such as treating asymptomatic subjects, but the cost of diabetes and its complications to the community may justify this approach. Longer-term follow up studies are needed to establish whether lifestyle and pharmacological interventions actually prevent type 2 diabetes or merely delay its onset.

The person with IGT represents a major challenge for general practitioners. Intervention at an early stage may reduce dramatically the risk of future diabetes and cardiovascular disease.

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