PEER REVIEWED FEATURE 2 CPD POINTS

Prediabetes
Preventing progression to diabetes

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Patients with prediabetes (impaired fasting glucose or impaired glucose tolerance) are at increased risk of developing type 2 diabetes and cardiovascular disease. Evidence supports intensive lifestyle management to help prevent or delay the progression to diabetes. Metformin has also shown benefit but is not approved for this indication in Australia.

KEY POINTS

- Prediabetes describes a state of impaired glucose regulation, where blood glucose levels are elevated above normal but not high enough to fulfil the diagnostic criteria for diabetes.
- Prediabetes is incidentally detected when assessing patients for type 2 diabetes.
- Prediabetes is defined as a plasma glucose level in the range 6.1 to 6.9 mmol/L after fasting (impaired fasting glucose); or the range 7.8 to 11.0 mmol/L at two hours after a 75 g oral glucose load (impaired glucose tolerance).
- People with prediabetes have an increased risk of developing diabetes, cardiovascular disease and premature death.
- Intensive lifestyle modification is effective in reducing progression of prediabetes to diabetes and should focus on weight loss, increased physical activity and dietary change.
- Pharmacological agents such as metformin can be considered in people with prediabetes, but this use is not TGA approved or PBS subsidised.

Prediabetes is a commonly used term to describe patients with elevated blood glucose levels that do not exceed the threshold to satisfy the diagnostic criteria for diabetes mellitus. It represents a state of impaired glucose regulation that may progress to diabetes.

The prevalence of prediabetes and diabetes is rising in Australia, in line with global trends. Australian predictions suggest that in adults over the age of 25 years, the prevalence of diabetes will increase from 7.4% in 1999–2000 to 11.4% in the year 2025, with associated implications for reduced quality of life and increased healthcare expenditure.[1] People with non-diabetic levels of hyperglycaemia have a risk of premature death that is intermediate between the risk of people with normal glucose tolerance and that of people with diabetes.[2] This is consistent with the concept that there is a continuous relation between increasing blood glucose levels and increased risk of cardiovascular disease and premature mortality.

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TABLE. CRITERIA FOR DIAGNOSING PREDIABETES AND DIABETES

Criterion	Normal	Prediabetes	Diabetes
Fasting glucose level (mmol/L)	<6.1	6.1–6.9 (IFG)	⩾7.0
Glucose level two hours after 75 g OGTT (mmol/L)	<7.8	7.8–11.0 (IGT)	⩾11.1

Abbreviations: IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test.

The implementation of effective strategies to prevent or delay progression to diabetes not only has the potential to make a significant impact on individual patients but also is essential in trying to curb the upward trend in diabetes prevalence at the population level. Prediabetes is best considered in clinical practice as an intermediate state of glucose dysregulation along a continuum for cardiometabolic risk. Overall management is directed at reducing total cardiovascular risk, with prevention of the progression to diabetes being one component of risk management.

Definition of prediabetes

Prediabetes is defined as a plasma glucose measurement in either of the two categories, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Testing should be done in the absence of severe illness.

The Australian Diabetes Society and Australian Diabetes Educators Association have adopted the WHO criteria for prediabetes, as follows.

- IFG is defined as a fasting plasma glucose level between 6.1 and 6.9 mmol/L
- IGT is defined as a plasma glucose level between 7.8 and 11.0 mmol/L at two hours after a 75 g oral glucose load (Table).[3]

The American Diabetes Association (ADA) uses a lower glucose range of 5.6 to 6.9 mmol/L as the criterion for IFG.[4]

In late 2014, glycosylated haemoglobin (HbA_{1c}) measurement was funded by Medicare as a diagnostic test for diabetes. The HbA_{1c} criterion for a diagnosis of diabetes is a level of 48 mmol/mol (6.5%) or more. The ADA considers an HbA_{1c} level in the range 39 to 46 mmol/mol (5.7 to 6.4%) as diagnostic of prediabetes, but this definition has not been adopted in Australia.[4,5]

Prediabetes is identified incidentally when patients are tested for type 2 diabetes. The RACGP recommends testing for diabetes in patients with symptoms or complications of diabetes or clinical signs of insulin resistance and also in asymptomatic individuals who are at high risk of type 2 diabetes.[6] Box 1 outlines some high-risk characteristics for adults who should be considered for diabetes testing.

The RACGP also recommends screening for the risk of diabetes in other patients every three years from the age of 40 years – or in Aboriginal and Torres Strait Islander people from the age of 18 years – using the Australian type 2 diabetes risk assessment tool (AUSDRISK; available at www.health.gov.au/internet/main/publishing.nsf/Content/diabetesRiskassessmentTool).[7] This screening tool assigns points for risk factors based on demographic, lifestyle and anthropomorphic features to predict the risk of developing diabetes over five years. Patients who score 12 or more are considered at high risk and should have fasting glucose level measured.[6]

Progression from prediabetes to diabetes

The increasing prevalence of type 2 diabetes is related to worldwide increasing trends in rates of obesity and physical inactivity.

1. SCREENING FOR DIABETES IN ASYMPTOMATIC ADULTS*

Consider screening for diabetes (with measurement of fasting glucose level, random glucose level, 75 g OGTT or HbA_{1c}) if:

- known IGT or IFG on previous testing
- history of cardiovascular disease
- age >35 years with high-risk ethnicity (e.g. Pacific Islands, Indian subcontinent, China)
- age >40 years with BMI ⩾30 kg/m^2 or hypertension
- a woman with history of GDM
- a woman with PCOS
- taking antipsychotic medication

Abbreviations: BMI = body mass index; GDM = gestational diabetes mellitus; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OGTT=oral glucose tolerance test; PCOS = polycystic ovary syndrome.

*Adapted from RACGP, Diabetes Australia. General practice management of type 2 diabetes (2014).[6]

These metabolic and lifestyle changes, in conjunction with genetic predisposition, insulin resistance and progressive beta-cell failure, result in levels of blood glucose rising through the prediabetes range towards the diabetes diagnostic threshold. The incidence of progression to diabetes has been as high as 10% per year in some studies of adults with prediabetes.[8] Over the long term, about half of those with prediabetes will develop diabetes, and a quarter will revert to having normal glucose tolerance.[3]

Management of prediabetes

Diabetes screening

Because of the risk of progression to diabetes, patients with IFG or IGT should be regularly tested for diabetes. The NHMRC *National Evidence Based Guideline for Case Detection and Diagnosis of Type 2 Diabetes* recommends retesting in these patients annually.[9]

Lifestyle management

Supporting evidence

Intensive lifestyle management has been consistently shown in prospective clinical

trials to be effective in preventing or delaying the conversion of prediabetes to diabetes. In the landmark US Diabetes Prevention Program, people with prediabetes were randomly allocated to a lifestyle-modification program, metformin treatment or placebo. Those in the lifestyle-modification program had the goal of achieving and maintaining 7% weight reduction through a healthy low-calorie and low-fat diet and at least 150 minutes weekly of moderate-intensity physical activity, such as brisk walking.[8] There was a 58% reduction in progression to diabetes over an average of 2.8 years of follow up in the lifestyle-modification group compared with the placebo group.[8] The beneficial effects of lifestyle on prediabetes were seen in both men and women, all racial and ethnic groups, and across all age groups.

Other large prospective studies have found similar reductions in diabetes incidence using lifestyle intervention. The Finnish Diabetes Prevention study also found an overall 58% reduction in diabetes incidence in the lifestyle-intervention group compared with the control group over four years in adults with IGT.[10] People in the lifestyle-intervention group were encouraged to achieve five goals: reduction in weight greater than 5%, reduction in total fat intake to less than 40% of energy consumed, reduction in saturated fat intake to less than 10% of energy consumed, increase in fibre intake to 15 g or more per 4200 kJ (1000 kcal) and moderate-intensity exercise for at least 30 minutes daily. The effects of the intervention on incidence of diabetes were more marked in people who made more pronounced changes to their lifestyle.

The earlier Da Qing Study found that diet and/or exercise intervention led to a significant decrease in diabetes incidence (31% reduction in the diet group, 46% reduction in the exercise group, 42% in the combined diet and exercise group) among people with IGT over six years compared with control subjects.[11]

Intensive lifestyle management was also shown to be effective in decreasing the rate of diabetes onset over longer term follow up beyond the intervention period in these three landmark studies, as follows:[12-14]

- 43% reduction in rate of diabetes onset at 20 years in the Da Qing Study
- 43% reduction at seven years in the Finnish Diabetes Prevention Study
- 34% reduction at 10 years in the US Diabetes Prevention Program Outcomes Study.

The US Diabetes Prevention Program found that weight loss achieved through diet and exercise was the primary factor resulting in reduced diabetes incidence in the lifestyle-intervention group, and that for every kilogram of weight loss, there was a 16% reduction in risk of progression to diabetes.[15] Increased physical activity was important in helping to sustain weight loss, and independently reduced diabetes risk even in those who did not lose weight.

Clinical practice recommendations

Australian clinical practice guidelines for lifestyle change in patients with prediabetes recommend aiming for (Box 2):[3,6]

- 5 to 7% weight loss (if overweight or obese)
- reduced total fat and saturated fat intake to less than 30% and less than 10% of total energy intake, respectively
- at least 30 minutes of moderate physical activity on most if not all days of the week (aiming for a minimum of 210 minutes per week of moderate-intensity exercise or 150 minutes per week of vigorous-intensity exercise).

It is recommended that a minimum of six months of lifestyle intervention be trialled before pharmacotherapy is considered.[3]

Lifestyle-modification programs should be tailored to individual patients, based on factors such as motivation and ability. Short-term goals can be set and subsequently intensified to encourage patients to make lifestyle changes. The involvement of other team members, such as dietitians, diabetes educators, exercise physiologists and physiotherapists, can help patients to develop and achieve realistic goals.[11]

2. MANAGEMENT OF PREDIABETES*

Lifestyle interventions (first-line)

Aim for:

- 5 to 7% bodyweight loss through diet and exercise (if overweight or obese)
- reduced intake of total fat to <30% and saturated fat to <10% of total energy intake
- 210 minutes per week of moderate-intensity physical activity or 150 minutes per week of vigorous-intensity physical activity

Pharmacological treatment

Options include:*

- metformin (first-line pharmacological option)
- acarbose
- rosiglitazone
- orlistat

Bariatric surgery

Options include:

- gastric bypass
- laparoscopic gastric banding

* None of these pharmacological agents are TGA approved or PBS subsidised for the treatment of prediabetes in Australia.

Pharmacological management

Several pharmacological agents have been shown to be effective in reducing the progression of prediabetes to diabetes in clinical trials. These include metformin, acarbose, rosiglitazone and orlistat.

Metformin

In the US Diabetes Prevention Program, the metformin intervention group (metformin 850 mg twice daily) showed a 31% reduction in diabetes incidence compared

with the placebo group.[8] Because intensive lifestyle intervention was significantly more effective at reducing diabetes incidence (58% reduction), it is generally recommended that lifestyle change be trialled first, before consideration of metformin therapy. Metformin may be particularly useful in people with a body mass index over 35 kg/m^2, age under 60 years and women with prior gestational diabetes.[16] Metformin has the strongest evidence base as pharmacological therapy for prevention of diabetes progression and has a strong track record for long-term safety. In Australia, however, metformin is not TGA approved or PBS subsidised for the treatment of prediabetes.

Other pharmacological agents

Other agents showing efficacy in diabetes prevention trials include acarbose, rosiglitazone and orlistat. Given the known side effects of these medications, their potential benefits and harms should be evaluated before initiating any of these agents for prediabetes treatment. Their use is not TGA approved or PBS subsidised for the treatment of prediabetes in Australia.

In the STOP-NIDDM trial, patients with IGT assigned to the acarbose group (100 mg three times daily) had a 25% reduction in diabetes incidence over 3.3 years of follow up compared with the placebo group.[17] Acarbose inhibits intestinal enzymes involved in the degradation of disaccharides, oligosaccharides and polysaccharides, and its use may be limited in many patients by the gastrointestinal side effects of flatulence and diarrhoea.

The antihyperglycaemic agent rosiglitazone (8 mg daily) used in patients with IFG and/or IGT in the DREAM study resulted in a 60% reduction in diabetes progression compared with placebo over three years.[18] There was a small but statistically significant excess in nonfatal congestive heart failure in the rosiglitazone group.

The XENDOS study found that the weight loss agent orlistat (120 mg three times daily) in combination with lifestyle change reduced diabetes incidence by 37% in patients who were obese and had either normal or impaired glucose tolerance, compared with lifestyle change alone over four years.[19] Mean weight loss was significantly greater in the orlistat group compared with the placebo group at the end of the study (5.8 *vs* 3.0 kg). Some patients may not tolerate orlistat because of its gastrointestinal side effects.

Bariatric surgery

Although diet and exercise are traditionally considered the mainstays of weight loss, patients can find it difficult to achieve and maintain reduced body weight in the longer term through these strategies. Average weight loss using intensive lifestyle change is 5 to 10% in clinical trials. Surgical approaches to weight loss can achieve 20 to 50% weight loss, and have improved rates of maintenance of the reduced body weight.

Australian guidelines recommend that bariatric surgery can be considered in selected individuals with morbid obesity at high risk of developing type 2 diabetes.[20] Two of the most common surgical procedures are roux en-Y gastric bypass and laparoscopic adjustable silicon gastric banding. Studies using gastric bypass procedures have been associated with a 99% prevention rate of diabetes in patients with IGT, and an 80 to 90% clinical remission rate of type 2 diabetes.[21] Gastric banding has been associated with a 50 to 60% clinical remission rate of type 2 diabetes.[21]

For some obese patients, after careful consideration of benefits and risks, bariatric surgery performed with the support of an experienced multidisciplinary team may be beneficial to reduce their long-term metabolic risk profile.

Conclusion

Effective treatment strategies are available for people with prediabetes to prevent and delay the progression to type 2 diabetes. These are an important component of management of patients with cardiovascular risk profile, in addition to treatment of hypertension and dyslipidaemia, and smoking cessation counselling. Intensive lifestyle management with diet and exercise to achieve weight loss is first-line treatment for patients identified as having prediabetes. MT

References

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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References

1. Backholer K, Peeters A, Herman WH, et al. Diabetes prevention and treatment strategies: are we doing enough? Diabetes Care 2013; 36: 2714-2719.
2. Barr EL, Zimmet PZ, Welborn TA, et al. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation 2007; 116: 151-157.
3. Twigg SM, Kamp MC, Davis TM, Neylon EK, Flack JR. Prediabetes: a position statement from the Australian Diabetes Society and Australian Diabetes Educators Association. Med J Aust 2007; 186: 461-465.
4. American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care 2015; 38 Suppl 1: S8-S16.
5. d'Emden MC, Shaw JE, Colman PG, et al. The role of HbA1c in the diagnosis of diabetes mellitus in Australia. Med J Aust 2012; 197: 220-221.
6. Royal Australian College of General Practitioners, Diabetes Australia. General practice management of type 2 diabetes – 2014–15. Melbourne: RACGP, Diabetes Australia; 2014.
7. Australian Government Department of Health. The Australian type 2 diabetes risk assessment tool (AUSDRISK). Canberra: Department of Health; 2010. Available online at: http://www.health.gov.au/internet/main/publishing.nsf/Content/diabetesRiskassessmentTool (accessed June 2015).
8. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-403.
9. Colagiuri S, Davies D, Girgis S, Colagiuri R. National evidence based guideline for case detection and diagnosis of type 2 diabetes. Canberra: Diabetes Australia, NHMRC; 2009. Available online at: https://www.nhmrc.gov.au/guidelines-publications/di17 (accessed June 2015).
10. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344: 1343-1350.
11. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997; 20: 537-544.
12. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet 2008; 371: 1783-1789.
13. Lindström J, Ilanne-Parikka P, Peltonen M, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006; 368: 1673-1679.
14. Diabetes Prevention Program Research G. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009; 374: 1677-1686.
15. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 2006; 29: 2102-2107.
16. American Diabetes Association. 5. Prevention or delay of type 2 diabetes. Diabetes Care 2015; 38 Suppl 1: S31-S32.
17. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002; 359: 2072-2077.
18. Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006; 368: 1096-1105.
19. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004; 27: 155-161.
20. Colagiuri R, Girgis S, Gomez M, Walker K, Colagiuri S, O'Dea K. National evidence based guideline for the primary prevention of type 2 diabetes. Canberra: Diabetes Australia, NHMRC; 2009.
21. Ferchak CV, Meneghini LF. Obesity, bariatric surgery and type 2 diabetes–a systematic review. Diabetes Metab Res Rev 2004; 20: 438-445.