Clinical presentations and diagnosis of diabetes

Philip Evans, Kate Sidaway-Lee, Suzane Ryan

Researchers, public health physicians and front-line clinicians, including GPs, are increasingly convinced that we are now in the midst of an epidemic (if not a pandemic) of diabetes mellitus. Diabetes prevalence rates are increasing across the world, particularly in developing countries, and an increasing number of people are being diagnosed in primary care. This article explores the clinical presentations and diagnosis of diabetes mellitus, focusing on type 2 diabetes. Approaches to preventing or delaying the onset of the condition in people with so-called "pre-diabetes" will be considered in a later module in this series.

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Learning objectives

After reading this article, the participant should be able to:

1. Describe the various forms of diabetes and how they differ.
2. Explain the process of diagnosing diabetes using HbA_{1c}.
3. Define the concept and reasoning behind the term "pre-diabetes".

Key words

- Diagnosis
- HbA_{1c}
- Pre-diabetes

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The number of people with diabetes mellitus continues to escalate and rates of diabetes are increasing across the world. The National Diabetes Services Scheme (NDSS) had 1 019 708 individuals registered with type 2 diabetes in June 2015 (NDSS, 2015). This is an approximate figure as not all people with the condition may be registered. Over the preceding 12 months, 65 463 people newly diagnosed with type 2 diabetes were registered in the program, which is the equivalent of 179 new registrants per day. The Australian Institute of Health and Welfare (AIHW) estimates that about 5% of Australians had type 2 diabetes in 2011–12 based on self-report measures (AIHW, 2013). This figure is set to rise.

Worldwide, there were thought to be 387 million people with diabetes in 2014 (International Diabetes Federation, 2014) and 90% of people with diabetes have type 2 diabetes (Whiting et al, 2011). Having diabetes means that an individual is more at risk of other disorders including cancer (Tsilidis et al, 2015). Moreover, the commonest cause of death in diabetes remains cardiovascular disease, and it accounts for 44% of all deaths in people with type 1 diabetes and 52% of deaths in people with type 2 diabetes (Morrish et al, 2001). Life expectancy is shortened considerably by both types of diabetes; for example, at age 55 the average male life expectancy is reduced by 3.6–11.5 years in people with type 2 diabetes, depending on risk factor status (Leal et al, 2009).

Allied to this increase in the prevalence of type 2 diabetes is the growing number of people with intermediate or borderline hyperglycaemia (often known as "pre-diabetes"). This condition carries a raised cardiovascular risk (Tabák et al, 2012), and the challenge to primary care still remains that of early diagnosis, effective intervention and, if possible, prevention of diabetes.

What is diabetes?

It is recognised that chronically raised blood glucose (hyperglycaemia) has numerous implications for the health of the individual. Diabetes mellitus is "a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, action or both." This definition by the American Diabetes Association (ADA; 2009)

illustrates the fact that diabetes is a syndrome with multiple causes. Apart from mothers who develop gestational diabetes when pregnant, the vast majority of non-pregnant people with diabetes fall into two main groups: type 1 and type 2 (ADA, 2015).

Type 1 diabetes is caused by an absolute deficiency of insulin, which is thought to be due to auto-immune destruction of pancreatic islet cells. Type 1 diabetes accounts for between 5% and 10% of all cases, and it is often diagnosed in younger people. Type 2 diabetes, however, is far more common (approximately 90% of all cases) and is usually diagnosed in people over 45 years of age, who are often obese or physically inactive. It is rapidly increasing in prevalence and is the driver for the current diabetes epidemic.

Unlike type 1 diabetes, type 2 diabetes is characterised by a relative insulin deficiency and is often associated with insulin resistance and features of the so-called "metabolic syndrome" (an increase in waist circumference and raised blood pressure, low HDL-cholesterol, raised plasma triglycerides or a raised blood glucose; Alberti et al, 2005).

Having previously been unknown in adolescents, type 2 diabetes is now being increasingly diagnosed in younger teenagers and young adults (Wilmot et al, 2010), and hence the likelihood of type 2 diabetes being confused with type 1 diabetes is increasing, as overlap in younger people is more common. Type 2 diabetes, however, still remains a disorder of later age and the largest increase in prevalence is in the over-65 age group, as the population as a whole ages (Wild et al, 2004). With diabetes in this particular age group comes increasing comorbidity and disability, as well as the complexities of managing people with multiple conditions and multiple medications. Type 2 diabetes is strongly dependent on ethnicity and is more common in South Asian and Aboriginal and Torres Strait Islander populations. The Aboriginal and Torres Strait Islander population is three times more likely to develop diabetes than the general population, while the South Asian population may develop diabetes at a lower BMI (Colagiuri et al, 2009).

Type 2 diabetes usually develops after a prodromal period of several years of gradually increasing glucose levels (Harris et al, 1992) and most people pass through a period of pre-diabetes before their hyperglycaemia reaches the diabetes threshold. Research published from the Whitehall II prospective study shows that people diagnosed with type 2 diabetes had a slow increase in their blood glucose levels over the 13 years of the study but that their blood glucose levels then rose rapidly in the 2 or 3 years preceding the diagnosis (Tabák et al, 2009). A recent study by the Cambridge team, following up their Ely study, suggested that this lead time for diagnosing diabetes has shortened from the 9–12 years suggested in the original US study in 1992 (Harris et al, 1992) to 3.3 years in 2012 (Rahman et al, 2012). This may of course be due to greater screening and awareness of diabetes on the part of primary care teams.

Diabetes is often asymptomatic until glucose levels rise, especially in older people (Abdelhafiz and Sinclair, 2013). Whatever the cause of the hyperglycaemia, however, the symptoms of diabetes usually include polyuria, urinary frequency and polydipsia (often waking up needing a drink in the middle of the night), all caused by an osmotic diuresis due to glycosuria. Other symptoms are weight loss (more often seen in type 1), tiredness, blurred vision and susceptibility to infections such as vaginal or penile candidiasis. Other individuals present with complications of diabetes such as gangrene or acute coronary syndrome. These complications can be disabling, even fatal, and include neuropathy, retinopathy, cardiovascular disease, sexual dysfunction and a significant impact on the individual's quality of life and social functioning. Even at diagnosis, around 25% of people with type 2 diabetes may already have complications (UK Prospective Diabetes Study [UKPDS] Group, 1998). It has also been noted at diagnosis that nearly half of the individual's insulin secretion has already typically been lost (UKPDS

Page points

1. Type 1 diabetes is caused by an absolute deficiency of insulin, which is thought to be due to auto-immune destruction of pancreatic islet cells.
2. Type 2 diabetes is characterised by a relative insulin deficiency and is often associated with insulin resistance and features of the so-called "metabolic syndrome".
3. Type 2 diabetes usually develops after a prodromal period of several years of gradually increasing glucose levels.
4. Diabetes is often asymptomatic until glucose levels rise, especially in older people.

Page points

1. Type 2 diabetes is generally considered to be a polygenic disorder. Diabetes with a monogenic, as opposed to polygenic, cause is seen much less frequently but nevertheless can present to GPs.
2. Maturity-onset diabetes of the young (MODY) is a monogenic autosomal dominant condition often causing hyperglycaemia in younger people and hence is likely to be diagnosed as either type 1 or early type 2.
3. Latent autoimmune diabetes of adulthood is a variant of diabetes which, like MODY, is increasingly being recognised as a diagnosis.
4. Diabetes can be diagnosed in primary care without specialist referral unless the person's condition is potentially life threatening. The use of HbA_{1c} as a diagnostic test was proposed by the World Health Organization in 2011.

Group, 1995), indicating that the progressive loss of insulin secretory reserve underpins the progression of diabetes with time, and hence the onset of symptoms.

Rarer causes of diabetes

Type 2 diabetes is generally considered to be a polygenic disorder. Diabetes with a monogenic, as opposed to polygenic, cause is seen much less frequently but nevertheless can present to GPs. For example, it is reasonable to assume that each GP will have at least one registered patient whose diabetes is due to maturity-onset diabetes of the young (MODY), although this is unlikely to have been recognised. MODY is a monogenic autosomal dominant condition often causing hyperglycaemia in younger people and hence is likely to be diagnosed as either type 1 or early type 2. The chromosomal defects and functional deficiencies have now been determined. The commonest form involves a mutation in one of the liver transcription factors known as hepatocyte nuclear factor (HNF)-1 alpha. Treatment options in these individuals are often dependent on the person's genetic sub-type (e.g. the effective use of low-dose sulphonylureas in people with HNF-1 alpha mutations [Murphy et al, 2008]).

Latent autoimmune diabetes of adulthood (LADA) is a variant of diabetes which, like MODY, is receiving more attention of late. It is relatively common and has been estimated to constitute up to 12% of people initially diagnosed with type 2 diabetes (Naik et al, 2009). It is frequently misdiagnosed and should be considered in younger people who do not fit the typical picture of type 2 diabetes (Appel et al, 2009).

Additional tests may be needed to assist in the diagnosis of diabetes sub-types: serum or urinary C-peptide levels will identify patients with an absence of, or minimal, insulin production; glutamic acid decarboxylase (GAD) antibodies and/or insulinoma antigen 2 (IA-2) antibodies are present in 90% of patients with type 1 diabetes; GAD antibodies are common in LADA, while GAD and IA-2 antibodies are absent in MODY.

MODY subtyping requires specialist review for genetic testing. As an illustration, in a young person who has been diagnosed with type 1 diabetes for 5 years, a relatively high urinary C-peptide creatinine ratio (UCPCR) would indicate the possibility of MODY rather than type 1 diabetes as endogenous insulin production has been maintained.

Diagnosing diabetes

Diabetes can be diagnosed in primary care without specialist referral unless the person's condition is potentially life-threatening and admission is necessary. Until recently, the diagnosis of diabetes and pre-diabetes was based upon blood glucose estimations, which could be random, fasting or after a glucose load (oral glucose tolerance test [OGTT]). Traditionally the OGTT was promoted as the gold standard for the diagnosis of diabetes and has been used extensively in epidemiological studies.

However, in 2011 the World Health Organization (WHO) proposed the use of HbA_{1c} as a diagnostic test for diabetes (WHO, 2011). The body recommended that a level of ≥48 mmol/mol (6.5%) was the cut-off for diagnosing diabetes and this advice was reiterated in the 2014–15 practice guidelines of the Royal Australian College of General Practitioners (RACGP; 2015) and the position statement of the Australian Diabetes Society (2015). The RACGP guidelines recommend two separate HbA_{1c} test results ≥48 mmol/mol (≥6.5%) for diagnosis confirmation. HbA_{1c} is known to reflect elevated levels of blood glucose over the preceding 2–3 months, and an analysis of a venous blood sample in an accredited laboratory using quality assurance tests is recommended. Point-of-care HbA_{1c} tests are not recommended for diagnosis unless their performance can match that of other laboratory methods.

HbA_{1c}, which does not need a fasting test, is far more practical than either fasting glucose tests or an OGTT and may well promote more widespread screening for diabetes.

Recently, however, an analysis by McDonald and Warren (2014) showed that in 63% of 188

people having a repeat HbA_{1c} within 14 days of being diagnosed, the second result was lower than the first, and in 40% of cases this follow-up test was below the diagnostic threshold. This would appear to justify a broader policy of repeating HbA_{1c} testing to help ensure that the diagnosis is correct. The implications of receiving a diagnosis of diabetes cannot be under-estimated.

In addition, it is imperative to note that there are some clinical situations when HbA_{1c} should not be used for diagnosis (see *Box 1*). Perhaps the most important situation of all is when considering a diagnosis of type 1 diabetes. There are also difficulties in using HbA_{1c} in people with haemoglobinopathies, anaemia or disorders causing an altered red cell lifespan, and there are ethnic differences as well (Venkataraman et al, 2012).

The introduction of diagnosis based on HbA_{1c} means that diabetes can now be diagnosed in several ways (see *Box 2*). There has been considerable discussion in the international diabetes community about this change (Bonora and Tuomilehto, 2011). Although potentially confusing for those of us working in primary care, the move to a single diagnostic and monitoring test in the form of HbA_{1c} may, in the long run, simplify issues of diagnosis and aid screening. It is worth noting that a single elevated HbA_{1c} level above 48 mmol/mol (6.5%) is accepted by Medicare as evidence of established diabetes, although this is not supported by current RACGP, ADA or WHO guidelines. Larger studies are needed in Australian general practice to determine in more detail the effect of this diagnostic change on clinical practice and in-practice prevalence rates.

Defining pre-diabetes

It is recommended that those people with an HbA_{1c} of 42–47 mmol/mol (6.0–6.4%) should be considered to be at high risk and to have the equivalent of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) – in other words, pre-diabetes. An HbA_{1c} in this range suggests an increased risk of developing type 2 diabetes that is greater than the risk estimated by the Australian type 2 diabetes risk assessment tool (AUSDRISK; Department of Health, 2013) alone. This simple scoring system was developed to predict incident diabetes based on demographic, lifestyle and anthropometric measures. Individuals with a "high" risk score of 12 or above are eligible for a health assessment that attracts a Medicare rebate (d'Emden et al, 2015).

In Australia, a value under 42 mmol/mol (6.0%) is considered to be "normal". By contrast, the ADA has suggested in the US that pre-diabetes should include people with an HbA_{1c} of 37–47 mmol/mol (5.7–6.4%).

Box 1. When HbA_{1c} must not be used as the sole test to diagnose diabetes.

As HbA_{1c} reflects glycaemia over the preceding 2–3 months, it may not be raised if blood glucose levels have risen rapidly. Examples of instances where HbA_{1c} should not be used as the sole test are:

- ALL symptomatic children and young people
- Symptoms suggesting type 1 diabetes at any age
- Diabetes symptoms of short duration
- People at high risk of diabetes who are acutely ill
- When the individual is taking medication that may cause a rapid rise in glucose levels (e.g. corticosteroids or antipsychotics)
- Acute pancreatic damage or pancreatic surgery
- During pregnancy

HbA_{1c} may be affected by any systemic condition causing reduced or increased red cell survival (e.g. splenomegaly, haemolytic anaemia and haemoglobinopathy), although many of these conditions will be detected by your local laboratory during the testing process.

Box 2. Diagnostic criteria for type 2 diabetes (Royal Australian College of General Practitioners, 2015).

- Fasting blood glucose ≥7.0 mmol/L (on two separate occasions)
- 2-hour post-prandial ≥11.0 mmol/L on oral glucose tolerance test (on two separate occasions)
- HbA_{1c} ≥6.5% (≥48 mmol/mol; on two separate occasions)

Page points

1. In general, the diagnosis of the intermediate hyperglycaemic states collectively known as "pre-diabetes" remains an area that is much debated.
2. The two most important features of pre-diabetes in primary care are the increased risk of cardiovascular disease and the increased risk of progression to type 2 diabetes.
3. Recently the AusDiab (Australian Diabetes, Obesity and Lifestyle) study data recorded that 16.4% of Australian adults had pre-diabetes.

This group has been termed "increased glycated haemoglobin" (IGH). This difference in approach persists today (ADA, 2015). It should also be observed that any of these glucose or HbA_{1c} cut-offs for the development of diabetes are, in effect, arbitrary thresholds along the continuum of hyperglycaemia as they are considered to be the level above which diabetic retinopathy (a specific diabetes-related microvascular complication) is more prevalent.

In general, the diagnosis of the intermediate hyperglycaemic states collectively known as pre-diabetes remains an area that is much debated. All these conditions have in common the fact that glucose and HbA_{1c} levels are raised, yet are not above the threshold diagnostic of type 2 diabetes. The two most important features of pre-diabetes in primary care are the increased risk of cardiovascular disease (CVD), which is two to three times that of normoglycaemic individuals (Coutinho et al, 1999), and the increased risk of progression to type 2 diabetes. Hence, there is the potential for prevention of both diabetes and CVD in this high-risk group.

The term pre-diabetes has been considered by some as being potentially misleading, as a large proportion of people with pre-diabetes do not progress to diabetes. The RACGP guidelines support the term pre-diabetes, separating it into two subgroups: IFG is defined as a fasting blood glucose (FBG) level of 6.1–6.9 mmol/L, with a 2-hour post-prandial level of 7.8 mmol/L; and IGT is defined as an FBG level of <7 mmol/L and a 2-hour post-prandial level of 7.8–11 mmol/L. These subgroups can coexist.

The AusDiab (Australian Diabetes, Obesity and Lifestyle) study data recorded that 16.4% of Australian adults had pre-diabetes (Twigg et al, 2007). Pre-diabetes carries an increased risk of progression to type 2 diabetes, although this can vary with ethnicity and other factors (Unwin et al, 2002). It is widely accepted that people with these conditions are at greater risk of both type 2 diabetes and cardiovascular disease (Coutinho et al, 1999) and interventions designed to prevent diabetes have in the main been targeted at this group. The ADA recently concluded that at least 70% of people with pre-diabetes will eventually progress to frank diabetes and it is estimated that by the year 2030, 470 million people globally will have pre-diabetes (Tabák et al, 2012).

However, a provocative recent article in the *British Medical Journal* (Yudkin and Montori, 2014) essentially questioned the whole premise of the diagnosis of pre-diabetes, suggesting that it is an example of over-diagnosis and is only "a risk factor for developing a risk factor" (type 2 diabetes).

Box 3. Case examples.

Example one

Martin is a 68-year-old individual with complex medical and psychological problems, including essential hypertension and morbid obesity (BMI, 43 kg/m^2). In 2011, he was screened for diabetes and found to have a fasting blood glucose of 6.5 mmol/L and was classified as having impaired fasting glucose. In 2013 he had symptoms of diabetes, and his HbA_{1c} was found to be 34 mmol/mol (5.3%), but a random glucose sample was 13.3 mmol/L at the same time. Further investigation of this discrepancy showed that his full blood count was abnormal and he was subsequently diagnosed with myelodysplasia, as well as being diagnosed with type 2 diabetes (on the basis of his blood glucose results rather than his HbA_{1c} results).

Example two

Adrian was diagnosed at age 42 with type 2 diabetes despite a normal BMI (24.8 kg/m^2). He was initially managed on metformin, but it became clear 3 years later that he had a strong family history (both his mother and sister had diabetes, both requiring insulin treatment). A family member was diagnosed with maturity-onset diabetes of the young (MODY) and Adrian was genotyped on advice from the local diabetes team. This test confirmed that he had MODY (hepatocyte nuclear factor-1 alpha mutation). His metformin was stopped and his diabetes is now well controlled on a small dose of gliclazide (40 mg), with his HbA_{1c} reducing from 60 to 40 mmol/mol (7.6% to 5.8%).

Case examples

Two case examples relating to diagnosis are presented in *Box 3*.

Conclusion

This module has reviewed the current state of play regarding diagnosis and clinical presentation of people with diabetes, focusing

on those with type 2 diabetes, as this is the most prevalent type seen in primary care. The more unusual types of diabetes such as MODY and LADA should not be forgotten and can be diagnosed in primary care with specialist help if needed. The implications of using HbA_{1c} as the single diagnostic and management test for diabetes have been explored. However, the precise impact of these changes on the number of people with a diagnosis of diabetes, and hence workload at a practice level, may vary. ■

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"A provocative recent article has questioned the whole premise of the diagnosis of pre-diabetes, suggesting that it is an example of over-diagnosis."

Online CPD activity

Visit www.pcdsa.com.au/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. According to current NDSS data, how many Australians are registered as having type 2 diabetes? Select ONE option only.

   A. 200 000
   B. 515 000
   C. 1 019 708
   D. 2 100 015

2. Which of the following is the commonest cause of death in people with type 1 diabetes? Select ONE option only.

   A. Accidents and falls
   B. Cancer
   C. Cardiovascular
   D. Hypoglycaemia
   E. Infectious disease

3. Which is the SINGLE MOST appropriate statement about type 2 diabetes? Select ONE option only.

   A. Less common than average in Aboriginal and Torres Strait Island (ATSI) and South Asian populations
   B. More common than average in ATSI populations but less common in South Asian populations
   C. More common than average in South Asian populations but less than average occurrence in ATSI populations
   D. More common than average in both South Asian and ATSI populations

4. According to a 2012 Cambridge study, what is the approximate lead time (in years) between the onset of increased blood glucose levels and a subsequent diagnosis of type 2 diabetes? Select ONE option only.

   A. 1
   B. 3
   C. 5
   D. 7
   E. 10

5. A 23-year-old with a strong family history was diagnosed with diabetes 7 years ago. A recent urinary C-peptide creatinine ratio is high.

   Which is the SINGLE MOST likely diagnosis based on this result? Select ONE option only.

   A. LADA
   B. MODY
   C. Pre-diabetes
   D. Type 1 diabetes
   E. Type 2 diabetes

6. A 49-year-old man has had an insurance medical with an HbA_{1c} result of 50 mmol/mol (6.7%). He has no symptoms of diabetes.

   According to a 2012 article by John et al, which of the following is the MOST appropriate action? Select ONE option only.

   A. Arrange a glucose tolerance test
   B. Diagnose pre-diabetes
   C. Diagnose type 2 diabetes
   D. Reassure him the result is satisfactory
   E. Repeat the HbA_{1c} within 2 weeks

7. In the 2014 study of 188 people with an initial HbA_{1c} above the diagnostic threshold for diabetes, what proportion of follow-up tests were normal? Select ONE option only.

   A. <1%
   B. 10%
   C. 25%
   D. 40%
   E. 75%

8. All international HbA_{1c} cut-off thresholds for the diagnosis of diabetes are based on the increased prevalence of which ONE of the following outcomes? Select ONE option only.

   A. All-cause mortality
   B. Cardiovascular events
   C. Cardiovascular mortality
   D. Diabetic neuropathy
   E. Diabetic retinopathy

9. According to a recent UK study using American Diabetes Association criteria, what is the estimated percentage of the population of England with pre-diabetes, as of 2011? Select ONE option only.

   A. 10%
   B. 25%
   C. 35%
   D. 50%
   E. 66%

10. In which ONE of the following situations is it most appropriate to use HbA_{1c} as a diagnostic test for new-onset diabetes? Select ONE option only.

    A. An 11-year-old girl with weight loss, vomiting and dehydration
    B. A 32-year-old woman who is 15 weeks pregnant
    C. A 55-year-old man who has undergone an emergency coronary artery bypass graft 24 hours earlier
    D. A 62-year-old man with a BMI of 37 kg/m^2, a blood pressure of 160/96 mmHg and hyperlipidaemia
    E. A 79-year old woman with polyuria who is taking high-dose prednisolone to treat her giant-cell arteritis