# 1 Classification, diagnosis and presentation

**Key points**

- The four major categories of diabetes are: Type 1, Type 2, gestational diabetes and other specific categories. The distinctions between Type 1 and Type 2 have been blurred latterly by clinically important syndromes, for example latent autoimmune diabetes of adults (LADA), which has some characteristics of Type 2, and Type 2 diabetes presenting with 'classical' Type1 diabetic ketoacidosis ('Flatbush'-type diabetes)
- Diabetes is diagnosed with laboratory fasting plasma glucose ≥7.0 mmol/l, random glucose ≥11.1 mmol/l or $HbA_{1c}$ ≥6.5% (48 mmol/mol)
- The differential diagnosis is widest in adolescents and young adults. Tests for islet-related autoantibodies, for example, those to glutamic acid decarboxylase, are of help in this group
- There is still no worldwide agreement on the biochemical diagnosis of gestational diabetes, but fasting plasma glucose values between 5.6 and 6.9 mmol/l are proposed
- The diagnosis of diabetes out of pregnancy is now based solely on fasting glucose values and $HbA_{1c}$. The glucose tolerance test is obsolete in non-pregnant adults
- Cumulatively, uncommon causes account for a significant proportion of patients, especially pancreatic and monogenic diabetes

## A PRACTICAL CLASSIFICATION OF DIABETES

The usual lists of types of diabetes, while comprehensive, are static and represent neither the frequency with which they are seen by general or even specialist practitioners, nor local differences in prevalence resulting from ethnicity and socioeconomic deprivation. So, for example, in the list of 'other specific types' of diabetes – a fascinating potpourri – the diabetes associated with a glucagonoma, seen perhaps a very few times in a lifetime by a specialist endocrinologist, is given the same apparent prominence as the much more common diabetes associated with pancreatic disease (mainly alcohol related). But before arriving at a practical discussion of some of the specific diabetes types – many of which must not be missed – we should consider the two major types, accounting for well over 90% of all cases: Type 1 and Type 2 diabetes.

In 1997, the American Diabetes Association proposed moving the classification towards one based on pathogenesis rather than treatment modality (even though the pathogenesis was not understood in full, either then or now). This resulted in, for example, a change in nomenclature from 'insulin-dependent diabetes' to 'Type 1 diabetes' (immune-mediated), and 'non-insulin-dependent' to 'Type 2 diabetes (insulin resistance with a variable contribution from insulin deficiency). Various other pathogenesis-based systems have been proposed, most recently one based on the centrality of β-cell stress,

*Practical Diabetes Care*, Fourth Edition. David Levy.

dysfunction or loss through multiple pathways (Schwartz *et al*., 2016). It is doubtful whether the clinician or patient will experience greater clarity from such complexity and for better or worse the current classification will remain.

## TYPE 1 DIABETES

'Classical' Type 1 diabetes (**Table 1.1**) is relatively uncommon and occurs in about one in 300 of a northern, white population, usually in children and pre-adolescents, though it can occur at any age (including the elderly). Its multiple previous names are – importantly – now obsolete. These include:

- Insulin-dependent diabetes
- Juvenile-onset diabetes
- IDDM (insulin-dependent diabetes mellitus). There has been a recent tendency to start using this term again, probably because in speech it is a euphonious abbreviation, in the same way as 'NIDDM' is for Type 2 diabetes. In practice it is coterminous with Type 1 diabetes, but 'IDDM' was dropped because not all patients with autoimmune diabetes require insulin treatment from the start, especially those with later-onset diabetes. The hazard is that 'IDDM' can become a cover-all term that includes insulin-treated Type 2 patients, thus dangerously de-emphasizing the continued need for insulin treatment without interruption in people with true Type 1 diabetes
- Ketosis-prone diabetes, ketosis being the simple but reliable clinical phenotype of insulin deficiency; but the spectrum of ketosis-prone diabetes is now wider than classical Type 1 diabetes

### Epidemiology; Type 1 diabetes in China

The epidemiology of Type 1 diabetes is fascinating, and mostly unexplained. It has a greater than 300-fold difference worldwide between countries of low incidence (e.g. China, Venezuela) and high incidence (e.g. Finland, much of northern Europe and Sardinia). Even within Europe the difference is tenfold, but there is a consistent difference between north (high incidence) and south (low), and west (high) and east (low). Very little is known about Type 1 diabetes in areas of low incidence but large populations, where the total burden may be high, but in Zhejiang, a rapidly developing province in south-east China, there has been a rapid increase in the under-fives (noted in many other countries too), and the mean age at diagnosis in children and adolescents fell by 1.6 years to 13 years over a short period between 2007 and 2013 (Wu *et al*., 2016). The phenotype of Type 1 diabetes in China is not well described but a large registry of Han Chinese from Guangdong (formerly Canton in South China, bordering Hong Kong and Macau) between 2000 and 2011 paints a striking picture (Yang *et al*., 2016):

- Older onset than in Europe: median age 28 years (compared with 14 in Germany, 9 in the USA), though with the same slight excess in males (54%)
- Patients are very slim (median body mass index (BMI) 20); 30% were underweight (BMI <20)
- There is a high prevalence of diabetic ketoacidosis at onset (50%), typical of countries where the incidence of Type 1 diabetes is low
- A significant proportion of patients had microvascular complications (retinopathy 8%, nephropathy 20%), implying a slow onset

**Table 1.1** Phenotypic features of Type 1 diabetes.

| Classical phenotypic characteristic | Modifiers | Importance for practitioners |
|---|---|---|
| White | Ethnicity and migration | In the UK, the incidence of Type 1 diabetes is probably almost as high in South Asian and African Caribbean people who have immigrated as in those of European heritage, but the overall prevalence is lower. Non-white ethnic groups at high risk of Type 1 diabetes include North Africans and Kuwaitis. White ethnic groups increasingly represented in the UK include the ex-Communist countries of Eastern Europe and the Baltic states (Estonia, Latvia and Lithuania).<br>Increasing distance eastwards and towards the equator is associated with a much reduced risk, so African people, South Americans and those from South-East Asia (especially China and Japan), have a very low risk of Type 1 diabetes – though there is always a small background risk which may be rapidly increasing (see below). |
| Onset in childhood and pre-adolescence | Age and secular trends | In high-risk countries, e.g. Scandinavia, peak incidence is at 10 years in girls, 13 in boys. After 16, the incidence falls rapidly and, thereafter, slowly over the next 20 years, at which point it merges into latent autoimmune diabetes of adults (LADA).<br>The incidence in the under 5s is increasing more rapidly than in older age groups, but absolute numbers in this age group are still low. |
| Onset | Age | Onset is acute with short preceding hyperglycaemia; with increasing age the clinical onset tends to be slower as the immunological assault on the β-cells weakens. |
| Lean body phenotype | Trends in obesity | Children are usually slim even before any weight loss that occurs before diagnosis. Older patients with antibody-positive diabetes (Type 1 diabetes or LADA) tend to be slightly overweight (e.g. mean BMI 26–27), less so than Type 2 patients (e.g. BMI 29–31), but it is not possible to make a presumptive diagnosis on body phenotype unless the patient is strictly of normal weight. |
| Ketosis | Age | Immunological attack on the β cells is most virulent in younger children; ketosis is a reliable indicator of insulin deficiency and, therefore, of presumed Type 1 diabetes. Beta-cell reserve is higher in older people developing Type 1 diabetes and ketosis may be intermittent or not apparent. |
| Microvascular complications | | Microvascular complications, especially retinopathy and neuropathy, are almost never present at the time of diagnosis. |
| Family history | | Powerful genetic factors are at play and nearly all patients will be HLA-DR3 and DR4 positive; but they do not affect the phenotype. Only about 5% of Type 1 patients have a positive family history in first-degree relatives (compare the variable but much higher rate in Type 2). |

**Practice point**

Younger people developing Type 1 diabetes are usually thin despite the increase in population levels of obesity.

Awareness of Type 1 diabetes is increasing in the general population and in parents of those diagnosed. Where there have been specific education programmes to further increase awareness, fewer children present in diabetic ketoacidosis.

The diagnostic problem may be most difficult at onset, especially in adolescents (see later) and older people, but management not based on a proper diagnosis can be problematic later in life, especially as most Type 1 diabetics can now be expected to live as long as non-diabetic people. Recognizing long-standing Type 1 diabetes in older people is the major difficulty (see **Chapter 14**). Typically, when insulin-treated patients move to a different part of the country or abroad, they can carry with them an array of obsolete diagnostic labels. The hazard – real – is that they will be reallocated on account of their age alone to 'insulin-treated Type 2 diabetes'. The hazards of this should not need pointing out, but it is a common scenario.

**Practice point**

Older insulin-treated people may have either Type 1 or Type 2 diabetes. This important distinction is blurred by the old label 'IDDM'. If there is any doubt, especially in the emergency situation, regard insulin-treated older people with long-standing diabetes as being Type 1 and fully dependent on insulin.

### Further clinical pointers to Type 1 diabetes

- Duration of insulin treatment: if continuous and started when the patient was under 30 years old, then Type 1 diabetes is highly likely
- A non-overweight, white person of any age treated with insulin alone should be considered to have Type 1 diabetes. Many patients now live without significant complications for 50 years or more (they are likely to be in their 60s and 70s). They often need only tiny doses of insulin (e.g. <20 units/day) but are fully insulin-requiring and will develop ketosis if insulin is withdrawn
- Continuing the treatment theme: someone on full insulin treatment (a regimen that covers night-time and meal times, without non-insulin agents) is very likely to have Type 1 diabetes (**Chapter 7**). Some Type 1 patients take metformin as well, either because they are overweight, with some degree of insulin resistance, or because they have polycystic ovarian syndrome, but these cases are unusual (**Chapter 7**)

## AUTOIMMUNE ASSOCIATIONS OF TYPE 1 DIABETES

There is a wide array of autoimmune conditions linked more or less strongly (and some speculatively because of their rarity) to Type 1 diabetes (**Box 1.1**). They pose a significant diagnostic problem because of their subtle symptoms and gradual onset, and there is a hazard that non-specific symptoms will be attributed to some aspect of the underlying diabetes.

**Box 1.1** Autoimmune conditions associated with Type 1 diabetes.

***Established organ-specific conditions***

- Autoimmune thyroid disease, especially Hashimoto's thyroiditis; Graves' hyperthyroidism much less common (~1% prevalence)
- Coeliac disease (clinical prevalence 1–8%, autoantibody positivity 8–14%)
- Addison's disease (clinical prevalence 0.5%)
- Pernicious anaemia (clinical prevalence 2–4%, much higher rates of positive parietal cell antibodies, 10–15% in children, 15–25% adults)

***Possible associations***

*Organ-specific*

- Primary ovarian failure
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Renal tubular acidosis
- Vitiligo
- Hypophysitis
- Myasthenia gravis
- Multiple sclerosis (speculative)
- Idiopathic thromobocytopenic purpura (speculative)

*Non-organ-specific*

- Juvenile rheumatoid arthritis
- Rheumatoid arthritis
- Sjögren's syndrome
- Systemic lupus erythematosus

Could there be an emerging associated autoimmune problem? is an important question always to bear in mind, regardless of the duration of Type 1 diabetes. The commonest are autoimmune thyroid disease, coeliac and Addison's disease. Up to 80% of patients will be hypothyroid at 20 years; this very high prevalence warrants annual thyroid function testing.

## TYPE 2 DIABETES

Because Type 2 diabetes is at least 10 times more common than Type 1, there is a tendency for clinicians to default to Type 2 when considering a diagnosis, especially in older and overweight or obese people. From the safety point of view, the tendency should be more to question whether any patient could have autoimmune diabetes. In adults, the need to alter our focus is seen increasingly commonly in the 'Flatbush' form of Type 2 diabetes that frequently presents with diabetic ketoacidosis, where the biochemical picture is indistinguishable from that of classical Type 1 diabetes-associated ketoacidosis. But in most cases there is little or no diagnostic difficulty (**Table 1.2**).

The over-representation of non-white ethnic groups in surveys of people with Type 2 diabetes is as striking as the over-representation of white people with Type 1. The importance of ethnicity as a risk factor for Type 2 diabetes cannot be overstated; data from the United Kingdom are shown in **Figure 1.1**.

**Table 1.2** Diagnosing Type 2 diabetes in adults.

| Classical phenotypic characteristic | Modifiers | Significance/Importance for practitioners |
|---|---|---|
| Ethnic minority (South Asian and African Caribbean in the UK) | Immigration<br>Increasing prevalence of obesity | In the UK the prevalence of Type 2 diabetes in South Asians is twice that of white people (14% vs 7%). That of African-Caribbeans is intermediate, about 10%. |
| Onset in middle age | Increasing obesity in youth | In the UK, Type 2 diabetes is diagnosed 6–7 years earlier in South Asian and African-Caribbean people than in white people.<br>Mean age of onset ~59 years (52 in South Asians and African-Caribbeans); compare the much younger age at onset in the USA in all ethnicities (mean ~45 years). Despite the increase in population obesity, Type 2 diabetes in adolescence is very uncommon in the UK, even in ethnic minority youth (Chapter 14) |
| Centrally obese phenotype | Increasing obesity | Visceral fat is critical; ectopic fat may have organ-specific effects (Chapter 13). |
| Absent ketosis | Factors increasing insulin resistance and decreasing β cell function, e.g. intercurrent infection or glucocorticoid use | If there is significant ketonuria, then treat as if insulin-deficient; absent ketonuria is characteristic of Type 2 and LADA |
| Microvascular complications | | If present, then very likely Type 2 diabetes (characteristic long asymptomatic prodrome with significant hyperglycaemia and associated metabolic syndrome abnormalities). However, micro- and macrovascular complications are much less common in ethnic minorities at diagnosis. |
| Family history | | Powerful. Risk is increased threefold if there is one parent with Type 2 diabetes, sevenfold if both, and fivefold if at least one sibling has diabetes. Overall prevalence of Type 2 diabetes: ~14% of people with family history (compared with 3% with no family history; USA data, Annis *et al*., 2005). |

*Source*: Winkley *et al*., 2013 (UK ethnicity data). Reproduced with permission of Springer.

## Latent autoimmune diabetes of adults (LADA): a valuable epidemiological concept, but of limited value in immediate clinical decision-making

This is a variable but increasingly common form of autoimmune diabetes, up to three times more prevalent than Type 1 diabetes, and therefore much more common than childhood-onset Type 1 diabetes. It is similar to other organ-specific autoimmune conditions, as it can occur throughout later life, and was first described in the

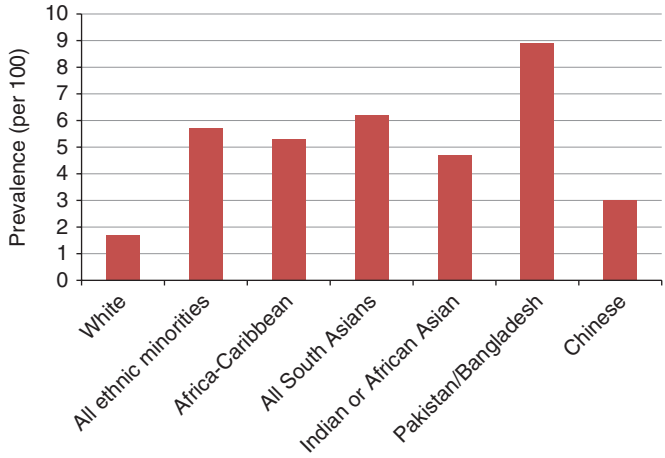


**Figure 1.1** Prevalence of Type 2 diabetes in the United Kingdom by ethnicity (age- and sex-standardized). *Source*: Holman *et al.*, 2011. Reproduced with permission of John Wiley and Sons.

mid-1970s, around the same time as the discovery of islet-cell antibodies. Its formal definition comprises:

- patients aged 30–70 years
- presence of diabetes-associated autoantibodies
- insulin treatment that did not start before six months after diagnosis.

It is only the last criterion, the arbitrary time frame within which insulin is started, that distinguishes LADA from Type 1 diabetes in older people. It is a retrospective diagnosis and does not help in the immediate characterization and management of newly-presenting patients, where clinical features and the presence of ketones indicate the need to start insulin treatment.

In the UK CARDS study, 7% of 'Type 2' patients were positive for GAD antibodies at recruitment, and by the end of the study, with a mean known duration of diabetes ~12 years, more than one-half were still not using insulin. Importantly, they were no more likely to have vascular complications compared with the insulin treated group (Hawa *et al.*, 2014). Its variable presentation and progress is due to at least five contributing domains (**Figure 1.2**).

In the Action LADA programme, Hawa *et al.* (2013) studied over 6000 adult patients across Europe. Findings are summarised in **Table 1.3**. Even in retrospective group comparisons there are few phenotypic differences between adult-onset Type 1 and LADA, the most striking of which is age (mean 42 years for Type 1 diabetes, 50 for LADA), and higher BMI (29 vs 26). The gender ratio is the same (50:50), as is systolic blood pressure and the lipid profile. However, the clinical profile is highly modified by the specific study. For example, in the ADOPT study of patients clinically diagnosed with Type 2 diabetes the LADA group, comprising 4% of the study population, had the same mean age as the Type 2 patients (57 years), but because this was a study in European and American subjects, BMI was overall higher (31-32) than in Action LADA (Zinman *et al.* 2004).

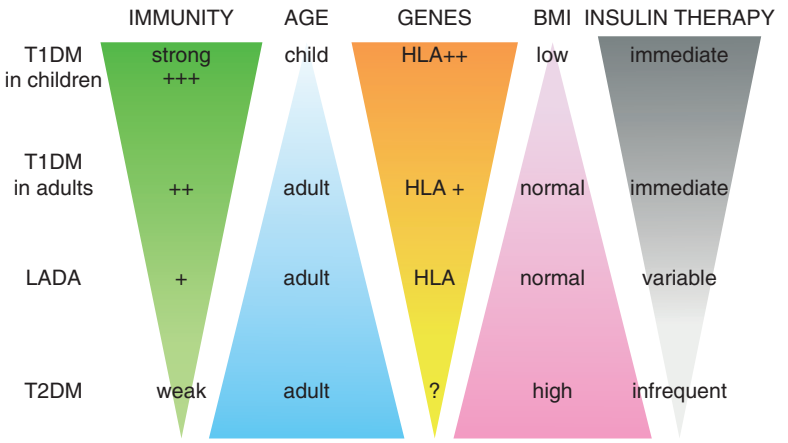


**Figure 1.2** The spectrum of autoimmune diabetes. Five important continuously variable domains interact to produce the broadening modes of presentation of autoimmune diabetes. *Source*: Leslie *et al.*, 2008. Reproduced with permission of John Wiley and Sons.

**Table 1.3** Characteristics of LADA in Europe.

| | |
|---|---|
| Mean age at diagnosis | 52 years |
| Males | 59% |
| Ethnicity | Caucasian 85%, Middle East 4.5%, Asian 2.5%, African 1.2%, other ethnicities 7.2% |
| Autoantibodies | Overall GADA positivity 91%<br>Other single autoantibody prevalences: IA-2A 5.0%, ZnT8A 2.3% (very low)<br>Two or more autoantibodies: 24.1% |

*Source*: Hawa ***et al.,*** 2013. Reproduced with permission of American Diabetes Association.

## Clinical diagnosis of autoimmune diabetes in older people

For clinical purposes, therefore, we need to adopt a basket of characteristics in order to diagnose autoimmune diabetes in older individuals presenting with hyperglycaemia:

- age >30 years
- subacute symptoms, duration usually under six months, for example, typical osmotic symptoms, unintentional weight loss, but not infections or blurred vision
- minor degree of weight loss
- lack of family history of diabetes
- presence of family or personal history of other autoimmune conditions
- in Europe, normal weight or overweight, rather than obese
- intermittent or 1+ or less ketonuria (analyse urine for ketones at every visit).

Clinicians will not receive a routine anti-GAD antibody (GADA) result from the laboratory for several weeks. GADA positivity confirms the diagnosis but 10% are GADA negative. Other diabetes-related autoantibodies (anti-IA-2A and ZnT8A) are not routinely available, and in any case much less frequently positive in later-onset compared with childhood-onset diabetes. If there is no ketonuria and blood glucose levels

are modest (e.g. around 15 mmol/l), start a trial of antidiabetic medication (metformin + secretagogue, either a sulfonylurea or repaglinide). The place of the DPP-4 inhibitors is not known in this clinical situation; they are weak secretagogues compared with a sulfonylurea (see **Chapter 10**). One of the major clinical features of LADA patients with poor β-cell reserve is a weak or absent response to non-insulin agents. If blood glucose levels are still in double figures about two weeks after starting a sulfonylurea, then this constitutes primary sulfonylurea failure and insulin treatment is needed. Because these patients are not especially insulin resistant, metformin monotherapy is unwise because the response may be minimal. Clinicians alerted to autoimmunity by requesting GADA tests that turn out to be positive tend to suggest earlier insulin treatment, though in many cases it is not needed: GADA positivity implies an autoimmune process affecting the islets, but not necessarily severe enough to cause insulin deficiency of a degree that mandates insulin treatment. Fasting insulin and C-peptide measurements have not been studied prospectively (see below for the clinical place of these tests).

**Practice point**

If clinicians learn that 'Type 2' patients are GAD antibody positive (about 1 in 20), they are more likely to suggest early insulin treatment, which may not be necessary. Observe carefully for signs of oral agent failure (poor glycaemic response to standard drugs, weight loss, intermittent ketonuria).

## The emerging role of C-peptide measurements: valuable to confirm or revise the need for insulin treatment in patients previously started on insulin treatment

C-peptide and insulin are secreted in equimolar concentrations from β-cells, so measuring C-peptide is potentially valuable in assessing endogenous insulin secretion in people taking insulin. There is broad agreement that a random non-fasting blood C-peptide measurement <0.2 nmol/l indicates absolute insulin deficiency. Assays are reliable and standardized and C-peptide is more stable than previously thought, up to six hours in serum gel or plain sample tube and up to 24 hours in whole blood collected in EDTA. A stimulated C-peptide measurement, commonly used in academic studies and clinical trials, is not necessary. Samples should be taken >90 minutes after a meal, and when blood glucose is >8 mmol/l. It is unreliable in the presence of hypoglycaemia (blood glucose <4 mmol/l). Finally, it must be interpreted with caution in the early stages (up to year 3) of diabetes. During a honeymoon period of Type 1 diabetes, C-peptide levels are likely to be high, and they can be transiently low in newly-diagnosed Type 2 diabetes that is accompanied by severe hyperglycaemia.

However, it still has value, not so much in formal diagnosis but in the common and difficult clinical situations where it is difficult to distinguish between Type 1, Type 2 and monogenic (MODY) diabetes in a patient taking insulin. In short, in certain common clinical circumstances it will answer the important therapeutic question: does this patient continue to need insulin? (**Table 1.4**) (Jones and Hattersley, 2013). Importantly, it is independent of the simple clinical characteristics (age, ethnicity, degree of obesity) that – as the data on LADA show – are increasingly unreliable in diagnosis. C-peptide measurements may also be of use as a simple biomarker of response to drugs, for example GLP-1 receptor agonists (see **Chapter 10**).

**Practice point**

Consider using a random blood C-peptide measurement to determine whether or not an insulin-taking patient with an unclear diagnosis some years before is truly insulin deficient. A value <0.2 nmol/l suggests severe insulin deficiency and the need to continue insulin treatment.

**Table 1.4** Clinical situations in which C-peptide measurement may help clinical decision making in insulin-taking patients.

| Clinical situation | C-peptide measurement (non-fasting 'random' blood measurement (nmol/l) or home postmeal urinary C-peptide-creatinine ratio (nmol/nmol) |
|---|---|
| Absolute insulin deficiency, i.e. Type 1 diabetes | <0.2 |
| Likely Type 1 diabetes/inability to achieve glycaemic control with non-insulin therapies | <0.6 |
| Suggests Type 2 or MODY in a patient with presumed Type 1 diabetes diagnosed >3–5 years previously | >0.2 |
| Consider MODY/Type 2 diabetes in young person at diagnosis | >1 |

*Source*: Jones and Hattersley, 2013. Reproduced with permission of John Wiley & Sons.

## ADOLESCENTS AND YOUNG PEOPLE

The differential diagnosis of diabetes is widest during adolescence and young adulthood, and while the typical acute onset of Type 1 diabetes is still the commonest presentation, the SEARCH study in the USA found that over 40% of cases were *not* Type 1 diabetes (Hamman *et al*., 2014):

- Type 1 diabetes and obesity (16% of cases)
- typical Type 1 diabetes (55%)
- typical Type 2 diabetes (26%)
- no autoimmunity or insulin resistance (10%):
  - monogenic diabetes (8%) – HNF-1α, glucokinase, HNF-4α
- secondary diabetes (uncommon in youth)
- other genetic types.

Formal diagnosis is critical in this group, and urgent specialist referral is needed.

## TYPE 2 DIABETES PRESENTING WITH DIABETIC KETOACIDOSIS ('FLATBUSH' DIABETES)

This is a now common but still perplexing presentation of Type 2 diabetes, first described in Africa in the 1960s and 1970s, but characterized in the 1990s in obese African-American men in their 30s living in the Flatbush area of Brooklyn, hence its informal name (Banerji *et al*., 1994). It presents with diabetic ketoacidosis, sometimes severe and indistinguishable from the ketoacidosis of Type 1 diabetes. However it is autoantibody negative and the acute insulin deficiency that precipitates ketoacidosis – and requires insulin treatment in the early stages – remits, often permanently. Patients often need insulin only for a short time (average 3½ months), and they are prone to hypoglycaemia

even on low doses of insulin shortly after discharge from hospital. Complete remission, defined as good glycaemic control on diet alone, occurs in 30–40% of cases, even if there is no weight loss. Relapse into diabetic ketoacidosis occurs but is uncommon. There are no long-term follow-up studies, which would be difficult because so many patients need no medication at all and are likely to be lost to follow-up. This presentation of Type 2 diabetes is becoming more common in the United Kingdom and practitioners in areas with ethnic minority patients will regularly encounter it. It is now a common presentation in African-American youth in the USA (it was described in 1987 in a group of Florida children, average age 13, but because they had a strong family history of diabetes presenting in a similar way, it was originally thought to be a form of MODY). There is also an isolated case report of a patient in India.

**Practice point**

'Flatbush' Type 2 diabetes in obese African or African-Americans frequently presents acutely as ketoacidosis, indistinguishable from the ketoacidosis of Type1. Discharge patients on insulin, but they need frequent follow-up, as most will not need insulin beyond a few months.

## TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS

Although Type 1 diabetes is still by far the commonest form of diabetes in USA youth, the SEARCH study in people under 20 found that 15% of diabetes cases in the white population were Type 2, increasing to 45% in Hispanics and 60% in African-Americans. Sixty percent were girls (Writing Group for the SEARCH Group, 2007). In the UK Type 2 diabetes in young people is very uncommon, around one-twentieth the incidence in the USA, and was not even described until 2002. Some of the difference in incidence is due to a higher proportion of ethnic minorities in the USA, and by population obesity levels, but there is likely to be ascertainment bias, as patients in late adolescence may not be captured by paediatric data collection. Many will be in the asymptomatic prodromal phase, whose duration is unknown, but, as in adults, likely to be several years.

Diabetes diagnosed on oral glucose tolerance test was found in only ~1% of obese white children over 12 years of age in Germany, and a similar proportion in overweight or obese 10–17 year olds in Michigan. Given the prevalence of obesity around 20%, Type 2 diabetes is undiagnosed in the majority of young people. In ethnic minority populations, systematic examination for axillary acanthosis nigricans, the classical cutaneous marker of insulin resistance, when added to elevated BMI and a positive family history, reliably identifies people at high risk; this straightforward clinical approach has been used in screening programmes in the USA (Lee *et al.*, 2013; see **Chapter 5**). To the list of risk factors should probably be added antipsychotic medication, which carries a two- to threefold increased risk of Type 2 diabetes that emerges soon after starting treatment, though the absolute risk still remains very low (Galling *et al.*, 2016).

In primary care, there is a good case for opportunistic screening, especially of overweight or obese children with one or more parents with Type 2 diabetes, using $HbA_{1c}$ rather than fasting glucose measurements (as recommended by the American Diabetes Association guidelines). However, we must not get too obsessed with glucose levels: elevated systolic blood pressure is the most prevalent treatable abnormality associated with insulin resistance in this age group.

**Practice point**

Type 2 diabetes in adolescence is uncommon in Europe, but be alert for it in young obese ethnic minority people with a positive family history, especially if there is axillary acanthosis nigricans.

## OTHER SPECIFIC TYPES OF DIABETES

### Fulminant diabetes

This is a fascinating form of antibody-negative diabetes (i.e. classified as Type 1B in contrast to the much more common antibody-positive form, Type 1A). It was first described in 2000. Most cases occur in South East Asian countries, especially Japan (where 5000–7000 cases have been reported), South Korea, the Philippines and Thailand, where autoimmune Type 1 diabetes is uncommon (Imagawa and Hanafusa, 2011). A handful of cases have occurred in Caucasians in France.

The phenotype is variable. Most cases occur in the third and fourth decades, and individuals are not usually notably thin. The onset is abrupt and the duration of symptoms usually less than a week before presentation. A viral precipitant is likely. Gastrointestinal symptoms are prominent and can result in a sometimes hazardous delay in diagnosis. Pancreatic enzymes are often elevated, suggesting exocrine involvement in the inflammatory process. Patients present in severe diabetic ketoacidosis (pH <7.1), often with blunted consciousness, and there is a significant mortality. Strikingly, the $HbA_{1C}$ at onset is nearly normal, around 6% (42), confirming the hyperacute onset. Any autoimmunity is feeble, and although certain HLA types are emerging, they are different from those of Type 1A diabetes. There are very few long-term studies, but in a nine-year follow-up in Japan, in spite of better glycaemic control than patients with acute-onset Type 1 diabetes and no difference in the prevalence of microalbuminuria, impaired renal function (eGFR <60 ml/min) was about twice as common (Takahashi *et al.*, 2017). Other striking differences from Type 1A diabetes are likely to emerge in future.

### Monogenic diabetes

The several forms of monogenic diabetes comprise only 1–2% of all cases of diabetes but they are mechanistically fascinating and clinically challenging, as they often present as only mildly atypical forms of Type 1 and Type 2 diabetes. Misra and Hattersley (2017) list features that should alert the clinician to monogenic diabetes:

- atypical presentations of Type 1 or Type 2 diabetes; they may coexist by chance with either of the major forms
- autosomal dominant family history (or maternal inheritance in the mitochondrial disorders)
- diagnosis within the first six months of life (possible mutations of the Kir6.2 and SUR1 subunits of the potassium channel of the pancreatic β cell)
- unusual clinical features, for example sensorineural deafness, acanthosis nigricans in the absence of obesity, partial lipodystrophy (muscular, thin limbs associated with elevated triglycerides and insulin resistance).

The most common phenotype is that of maturity-onset diabetes of the young (MODY), broadly divided into glucokinase and transcription factor types, both showing autosomal dominant inheritance.

### Glucokinase MODY

In the β-cell, glucokinase serves as a glucose sensor and loss-of-function mutations result in glucose still being tightly regulated but at a slightly higher level than in the non-diabetic person, with fasting levels typically between 5.5 and 8 mmol/l, and modest peak increases, usually <5 mmol/l, on a glucose tolerance test. Onset is at birth but it is a benign form of diabetes and is usually diagnosed as either Type 2 diabetes or during screening for gestational diabetes. Hyperglycaemia does not show the typical progression seen in Type 2 diabetes and microvascular complications are rare. Glucokinase MODY and Type 2 diabetes are both strongly familial but patients with MODY are usually not obese and do not have multiple insulin resistance characteristics. It is important to make a secure diagnosis. Insulin treatment is often started because patients are young and not obese, but is usually unsuccessful in reducing the relatively mild hyperglycaemia.

### Transcription factor MODY

Transcription factor MODY is usually caused by mutations in the hepatic nuclear factors 1A and 4A (*HNF1A* and *HNF4A* genes). Together they comprise nearly three-quarters of all cases of MODY. Again the defect involves the β-cell, both its development and function. It usually presents in early life, between the ages of 10 and 30. Fasting glucose is often normal at first, but on glucose tolerance testing larger excursions in glucose occur (>5 mmol/l) than in glucokinase MODY. While patients are not especially obese, they are prone to microvascular and macrovascular complications, and require pharmacological treatment.

## Type 2 diabetes in South East Asia

The population of South East Asia is huge. There is high awareness of the growing numbers of people with diabetes, and some epidemiology, but strikingly little data on detailed phenotype and specific responses to interventions, other than the Da Qing study of intensive lifestyle modification in prediabetes (see **Chapter 9**). We should not uncritically extrapolate findings in Europeans to South East Asian groups or individuals. Patients are clinically often highly sensitive to medication and their side-effects in all therapeutic areas, and some drugs are formulated at lower doses for use in Asian patients.

Baseline characteristics of a large group of newly-diagnosed Type 2 Chinese people recruited to a trial of metformin and acarbose were reported by Yang *et al*. (2014) (**Table 1.5**). They are young and, although average BMI is not especially high, there is a consistently increased risk of diabetes at any BMI value compared with Europeans and Japanese on account of increased visceral adiposity (**Figure 1.3**). Blood pressure is strikingly normal, though the lipid profile is similar to that of newly-diagnosed Europeans. There are few large clinical studies of drug treatment in Chinese, other than registration trials of new agents, but clinically South East Asian people respond well to insulin and secretagogues, consistent with a higher insulin sensitivity (and larger postprandial glucose excursions) due to lower insulin resistance and a greater deficit in β-cell function (Ma and Chan, 2013). Alpha-glucosidase inhibitors are effective and well-tolerated (see **Chapter 10**).

**Practice point**

South East Asian patients are at higher risk of Type 2 diabetes than Europeans or Japanese. Lifestyle interventions in prediabetes (Da Qing study) are highly effective. There is visceral adiposity but in clinical practice patients are sensitive to insulin and secretagogues.

**Table 1.5** Characteristics of newly-diagnosed Chinese Type 2 patients.

| | |
|---|---|
| Age (years) | 50 |
| BMI | 26 |
| Waist circumference (cm) | 92 (men), 86 (women) |
| Blood pressure | 124/80 |
| *Lipid profile* | |
| Total cholesterol (mmol/l) | 5.5 |
| Triglycerides (mmol/l) | 2.3 |
| HDL cholesterol (mmol/l) | 1.23 |
| LDL cholesterol (mmol/l) | 3.1 |
| $HbA_{1c}$ (%) | 7.5 (58) |

*Source*: Yang *et al.*, 2014. Mean values are quoted.

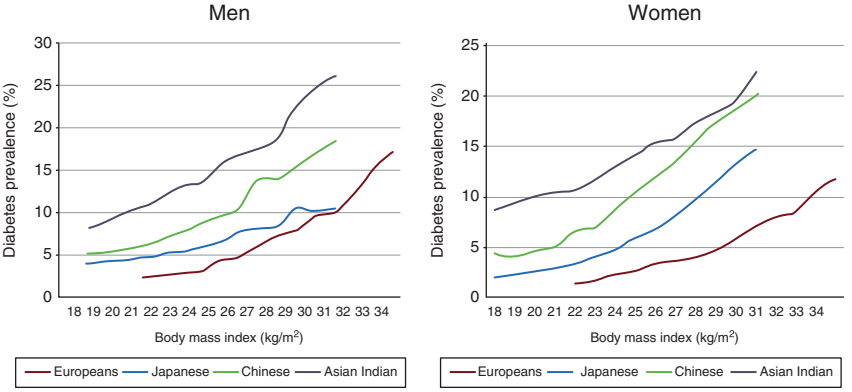


**Figure 1.3** The prevalence of Type 2 diabetes in four ethnic groups. In both men and women, at a given BMI, the prevalence is Asian Indian > Chinese > Japanese > European. Chinese have a two- to threefold increased risk compared with Europeans. However, in comparison with Asian Indians, Chinese are less insulin resistant. *Source*: Nyamdorj *et al.*, 2010. Reproduced with permission of Nature Publishing Group.

## DISEASES OF THE EXOCRINE PANCREAS

This important group includes:

- acute pancreatitis
- chronic pancreatitis (including chronic calcific pancreatitis – which includes 'tropical pancreatitis')
- genetic and secondary haemochromatosis
- other rare infiltrative diseases, for example sarcoidosis
- cystic fibrosis
- adenocarcinoma of the pancreas
- surgical resection.

Parenchymal disease of the exocrine pancreas frequently results in diabetes as the exocrine and endocrine elements of the pancreas are admixed. Islets are concentrated more in the tail of the pancreas and diabetes usually occurs after surgical excision of the distal pancreas. The diabetes is insulin-requiring, because of loss of β-cells, but is also notoriously difficult to control. One reason may be the loss of α-cells in the inflammatory process, which removes glucagon as the first-line counterregulatory defence against hypoglycaemia. Conversely, diabetic ketoacidosis, which is exacerbated by high glucagon levels, is less common. Patients are often thin, and the relative lack of adipose tissue may contribute to less severe ketosis.

Pancreatic insufficiency in people with Type 2 diabetes but who have no evidence of chronic pancreatic disease is increasingly recognized, but the true prevalence of clinical pancreatic insufficiency is probably low – there are many studies showing high rates of abnormal laboratory tests, for example, low faecal elastase, the significance of which is debated. But always be alert to clinical pointers of insidious exocrine insufficiency, for example weight loss, non-specific bowel symptoms and increasingly frequent hypoglycaemia in the face of reduced insulin doses. Indian patients, both Type 1 and 2, may be at particularly high risk: around one-third of a large group had low faecal elastase, compared with only 5% of controls (though these high proportions are described in non-Asian groups too) (Shivaprasad *et al*., 2015).

## Acute pancreatitis

Type 2 diabetes is itself associated with an increased risk of acute pancreatitis. Alcohol and gallstones are by far the commonest causes, but severe hypertriglyceridaemia is a common cause in South Asian patients with metabolic syndrome characteristics, when it is often associated with poorly-controlled Type 2 diabetes (see **Chapters 12 and 13** and Levy, 2016). Although the highest risk occurs with triglyceride levels >5–10 mmol/l, general population studies show a gradually increasing risk above triglyceride levels of 2 mmol/l, for example a threefold increased risk at 3–4 mmol/l compared with <1 mmol/l (Pedersen *et al*., 2016).

Transient hyperglycaemia after acute pancreatitis is common and does not always settle after discharge; about 15% of patients will develop diabetes during the first twelve months and the risk of diabetes triples over three years. Patients who have had acute pancreatitis should have regular $HbA_{1c}$ measurements.

Countless drugs have been anecdotally associated with acute pancreatitis. The DPP-4 inhibitors (gliptins) and GLP-1-receptor agonists were suspected as culprits, but the risk, if any, is very small (see **Chapter 10**). However, these agents should not be given to patients with a history of acute or chronic pancreatitis. The textbook drugs (thiazides, glucocorticoids and the oral contraceptive) in practice almost never cause acute pancreatitis.

**Practice point**

About 1 in 6 patients will develop diabetes in the first year after an episode of acute pancreatitis. Where possible, monitor $HbA_{1c}$ levels every 3–6 months.

## Chronic pancreatitis

Alcohol is the commonest cause of chronic pancreatitis in the west but there is increasing interest in a variety of autoimmune forms, for example as part of the broadening spectrum of IgG4-related diseases. In alcohol-associated cases exocrine insufficiency dominates, with variable degrees of glucose intolerance. Associated liver disease also contributes to

the hyperglycaemia. Pancreatic calcification on plain abdominal radiographs is characteristic; larger pancreatic stones are typical of tropical pancreatitis.

**Practice point**

Diabetes associated with chronic pancreatitis is usually insulin-requiring and often difficult to control.

### Haemochromatosis

Genetic haemochromatosis due to a characteristic C282Y mutation in the *HFE* gene is common in white northern populations. It rarely presents as diabetes, though impaired glucose tolerance on glucose tolerance tests during pregnancy, especially in a non-obese white subject, should raise the suspicion. The associated diabetes is not clearly either pancreatic or mediated through insulin resistance, though many patients eventually require insulin.

### Cystic fibrosis

Cystic fibrosis-related diabetes occurs in ~50% of patients reaching adulthood. It is a distinct form of non-autoimmune diabetes that has some characteristics of Type 2 diabetes, but there is a strong genetic component to the diabetes separate from the genetic defect of cystic fibrosis itself. There is some hope, though little evidence, that insulin therapy may help lung function in cystic fibrosis but there may be a threshold effect of glucose – around 8 mmol/l – associated with developing impaired pulmonary function. The diabetes is usually insulin sensitive, suggesting residual β-cell function, and rarely presents as diabetic ketoacidosis. The Cystic Fibrosis Association (USA) recommends insulin treatment when diabetes is diagnosed, but comparative trials are needed to establish the value of glycaemic control on lung function (Onandy and Stolfi, 2016).

### Pancreatic carcinoma

This is a fearsome condition in which diabetes is nearly always a secondary consideration. Type 2 diabetes probably carries an increased risk of pancreatic adenocarcinoma; new-onset Type 2 diabetes is associated with an eightfold increased risk and diabetes can remit after successful surgery. Insulin treatment is associated with a much higher risk than either sulfonylureas or metformin, but a causal link with any specific treatment has not been established. The diabetes is widely assumed to be caused by pancreatic destruction, but tumours usually occur in the head of the pancreas where there are few β-cells. The often small tumour size hints at another process and there is some evidence that the diabetes is serologically mediated through insulin resistance and not β-cell dysfunction (Lu *et al*., 2015).

### Other genetic syndromes associated with diabetes

Examples include Turner syndrome (in which there is a greatly increased risk of both Type 1 and 2 diabetes), Klinefelter syndrome, Friedrich ataxia, Huntington disease and myotonic dystrophy.

### Endocrinopathies associated with hormones mediating insulin resistance

These are, appropriately, at the end of the list, as they only exceptionally rarely present as diabetes; the features of the underlying endocrine disease are usually much more prominent. Examples include acromegaly (growth hormone), Cushing's disease or

syndrome (cortisol), phaeochromocytomas (catecholamines, especially noradrenaline) and glucagonoma. Several studies have uncovered excess cortisol in up to 10% of people with poorly-controlled Type 2 diabetes. The significance of these findings is disputed but vigilance is needed, as the gross textbook phenotype of Cushing's is just that, and many patients will not present with striae, buffalo humps or osteoporotic fractures. More promising therapeutically is the relatively recent discovery of the complexity of intracellular cortisol metabolism and its importance in obesity and Type 2 diabetes. For example, the enzyme 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1), present in adipose tissue and the liver, generates intracellular cortisol from cortisone and is a potent stimulator of adipogenesis, giving rise to the colourful concept of 'Cushing's disease of the omentum'. A few years ago there was intense pharmacological interest in the blood glucose-lowering effects of selective blockers of this pathway. In Phase 2 clinical studies $HbA_{1c}$ levels fell by ~0.5%, associated with some weight reduction and improvement in lipid profiles (Rosenstock *et al*., 2010), and another agent improved fatty liver in non-diabetic subjects. The development of this potentially valuable group of drugs for Type 2 diabetes has stalled recently. Protocols for the laboratory diagnosis of endocrine disorders associated with hypertension are outlined in **Chapter 11**.

**Practice point**

Among the long list of rare endocrine disorders associated with Type 2 diabetes, very few will present with hyperglycaemia. There is much interest in cortisol overproduction in adipose tissue and the liver that may contribute to Type 2 diabetes and the metabolic syndrome, but nothing yet of therapeutic value.

## New-onset diabetes after transplantation (NODAT)

This is a common and important multifactorial form of diabetes. It is not clear whether it is a distinct form of diabetes or, more likely, a form of Type 2 diabetes accelerated by multiple factors caused by transplantation (Sharif and Cohney, 2016). It shares features of both insulin resistance and β-cell failure. Drugs, especially the calcineurin inhibitors (ciclosporin and tacrolimus) contribute; sirolimus is under suspicion. Ascertainment is difficult. Most patients do not have standardized formal diabetes assessments before transplantation; in both end-stage renal and liver diseases, many patients have complex states of dysglycaemia before transplantation. But transplantation is undoubtedly an added risk: a year after renal transplantation, 10–20% have diabetes on a glucose tolerance test, compared with only about 5% of non-transplanted patients. It carries a poor prognosis for organ and patient survival and cardiovascular events, with up to threefold increased risks. All vascular risk factors must be rigorously managed and joint management with the transplant team would be wise, though not always achieved in the real world. There are no documented major interactions between modern antirejection drugs and non-insulin agents for the treatment of glycaemia but it is always wise to check before prescribing; compromise of a transplanted organ is always more important than modest short-term hyperglycaemia.

**Practice point**

New-onset diabetes after transplantation is common. Always additionally check $HbA_{1c}$ in transplant patients when requesting routine laboratory tests.

## PREGNANCY AND GESTATIONAL DIABETES MELLITUS

Hyperglycaemia of some degree occurs in about 1 in 6 pregnancies worldwide, of which one-sixth are probably newly-diagnosed diabetes, mostly Type 2, and the remainder gestational diabetes mellitus (GDM).

GDM is hyperglycaemia that does not meet the criteria for frank diabetes with onset or first recognition during pregnancy. The diagnosis is independent of treatment modality and GDM must be distinguished from pregnancy in patients with pre-existing Type 1 or 2 diabetes, and the uncommon cases of Type 1 or Type 2 diabetes newly diagnosed during pregnancy. Risk factors for GDM are shown in **Box 1.2**. Type 2 diabetes is increasing in women of childbearing age, especially in ethnic minority groups, but is still relatively uncommon. The importance of prepregnancy counselling in patients with known diabetes is widely recognized but systematic implementation is elusive and, even in Type 1 diabetes, around 30% of pregnancies in the United Kingdom are unplanned, and up to 50% are unplanned in the USA (see **Chapter 14**). Curiously, prepregnancy counselling in Type 1 diabetes is less effective than in Type 2 (Dozio, 2016).

If developing the criteria for the laboratory diagnosis of diabetes itself has been troublesome, the difficulties pale into insignificance beside the tortured disagreements that still haunt the quantitative definition of GDM. To both outsiders and patients this must seem incomprehensible; after all, GDM was first identified in the mid-1960s. However, there are recommendations that are likely to come into widespread use in some high-resource health systems (**Box 1.3**) (Hod *et al*., 2015)**.** About 50% of pregnant women have one or more risk factors for GDM and this very high prevalence has encouraged the consensus that all women should be tested. Although morbidity lies on a continuum of glucose levels, with no obvious inflection points, GDM carries risks for the mother (caesarean deliveries, birth trauma, hypertensive disorders of pregnancy, including pre-eclampsia, and of course, Type 2 diabetes), and for the foetus and offspring (macrosomia, shoulder dystocia and other birth injuries, respiratory distress, hypoglycaemia, polycythaemia and hyperbilirubinaemia; in the longer term, increased risk of obesity, metabolic syndrome, dysglycaemia and diabetes). In 2010, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) proposed universal screening with a 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks, or at any other time during pregnancy. Despite widespread support, there is still concern about

**Box 1.2** Risk factors for GDM.

- Ethnicity (in the UK South Asian – especially India, Pakistan or Bangladesh; Black Caribbean; Middle East)
- Older age
- High parity
- Overweight and obesity; short stature
- Excessive weight gain in the index pregnancy
- Polycystic ovarian syndrome
- History of diabetes in first-degree relatives
- History of poor pregnancy outcomes (macrosomia, foetal loss)
- Pre-eclampsia
- Multiple pregnancy

*Source*: Hod *et al*., 2015. Reproduced with permission of John Wiley & Sons.

**Box 1.3** Pregnancy and diabetes.

***Protocol in high-resource settings***

- Screen for diabetes in pregnancy at booking/first trimester, using fasting or random plasma glucose or $HbA_{1c}$
- If negative, perform 75-g 2-h oral glucose tolerance test at 24–28 weeks

*Diagnosis of overt diabetes in pregnancy:*

- FPG ≥7.0 mmol/l (126 mg/dl), ± 2-h value on oral glucose tolerance test ≥11.1 mmol/l (200 mg/dl) *or*
- Random plasma glucose ≥11.1 mmol/l (200 mg/dl), associated with signs and symptoms of diabetes
- $HbA_{1c}$ ≥6.5% (48) (ADA recommendation)

*Diagnosis of GDM*

These criteria are considered appropriate for different ethnicities, with perhaps the exception of Chinese people. One or more of:

- FPG 5.1–6.9 mmol/l (92–125 mg/dl)
- 1-h post 65-g oral glucose load ≥10 mmol/l (180)
- 2-h post 65-g oral glucose load 8.5–11.0 (153–199)

Elevated random plasma glucose in early pregnancy (at booking); value of ≥7.5 mmol/l is better than maternal age or BMI in predicting GDM (Meek *et al*., 2016).

*Source*: Hod et al., 2015. Reproduced with permission of John Wiley & Sons.

the poor clinical predictive value of these criteria, while at the same time increasing the risk of overdiagnosis and overtreatment. We are left with a plethora of protocols in use in different countries and in individual institutions. Critically, the historical two-stage diagnostic process established for many years in the USA is still recommended, and this will be the major barrier to wider acceptance of the IADPSG cut-offs.

## DIAGNOSIS OF DIABETES IN NON-PREGNANT ADULTS (BOX 1.4)

The oral glucose tolerance test is obsolete for diagnosing diabetes in the non-pregnant adult, and although its proposed demise was well-signalled for years, it is still frequently requested. Laboratory fasting venous plasma glucose or whole blood $HbA_{1c}$ are the only accepted measurements, though measurements using laboratory-standard point-of-care devices (e.g. HemoCue) are acceptable. Measurement of $HbA_{1c}$ is now so reliable that a DCCT- or IFCC-traceable $HbA_{1c}$ of 6.5% (48) or above can and where available should be used to diagnose diabetes. The epidemiological evidence for the cut-point of 6.5% is the same as that for fasting plasma glucose values: the prevalence of definite retinopathy diagnostic of diabetes (moderate non-proliferative or worse) is vanishingly small at lower values. There is voluminous data indicating that cardiovascular disease risk begins to climb from a much lower baseline within the non-diabetic range, but this is a continuous spectrum, so diagnostic criteria cannot be established. The use of diagnostic $HbA_{1c}$ values has rapidly increased in well-resourced countries, and was adopted by the WHO in 2011.

**Practice point**

In the absence of symptoms, fasting plasma glucose ≥7.0 mmol/l or random $HbA_{1c}$ ≥6.5% (48) is diagnostic of diabetes. No further tests are required.

**Practice point**

The oral glucose tolerance test is troublesome, time- consuming and expensive; it is obsolete apart from its important place in obstetric practice.

**Box 1.4** Diagnosis of diabetes.

- $HbA_{1c}$ ≥6.5% (48 mmol/mol) *or*
- Fasting plasma glucose ≥7.0 mmol/l (126 mg/dl)
- Random plasma glucose ≥11.1 mmol/l (200 mg/dl) in the presence of symptoms (this is a highly abnormal value, but like all diagnostic measurements, must be measured in a laboratory and not with home blood glucose testing devices)
- The oral glucose tolerance test is no longer used for diagnosis except in obstetric practice
- Where the initial result is close to the diagnostic value, a repeat measurement is recommended. If two tests have been initially done, and one is above the cut-point, then this should be the one to be repeated
- The simplicity of these tests compared with the OGTT means that they are simple to repeat in practice. Diagnostic $HbA_{1c}$ is especially valuable in:
  - Hospitalized patients where intercurrent illness usually increases insulin resistance resulting in transiently high glucose levels but a strictly normal $HbA_{1c}$ ('stress hyperglycaemia')
  - Patients who have deliberately lost weight when they recognize symptoms, and who then present with normal fasting glucose values.

## PREDIABETES

A term as fraught and difficult as the 'metabolic syndrome' (of which it is a component; see **Chapter 13**); in both instances, furious debates about the diagnostic criteria have dominated the discussion rather than their clinical significance. The world cannot even agree a cut-point value for 'prediabetes', let alone accurately guide prognosis for progression to diabetes, variously estimated at 4–9% annually (diagnostic glucose criteria are shown in **Box 1.5**). Nevertheless, we can at least be grateful that the oral glucose tolerance test-defined 'impaired glucose tolerance' (and its contorted partner 'impaired glucose tolerance' with 'impaired fasting glucose') has now disappeared. A huge proportion of the population of the USA has prediabetes on either fasting glucose levels or $HbA_{1c}$ – one-third of those over 20, and one-half of those over 65 (Bansal, 2015). Nevertheless, for an individual it is a valuable portal to the recognition of the cluster of insulin-resistance characteristics that might predispose to premature cardiovascular disease, and may well be associated with significant health problems of more pressing

**Box 1.5** Biochemical definitions of prediabetes.

*World Health Organization (WHO)*
Fasting plasma glucose 6.1–6.9 mmol/l (110–125 mg/dl)

*American Diabetes Association*
Fasting plasma glucose 5.6–6.9 mmol/l (100–125 mg/dl) *or*
$HbA_{1c}$ 5.7–6.4% (39–46 mmol/mol)

concern, especially hypertension, non-alcoholic fatty liver disease and obstructive sleep apnoea. The place for glucose-lowering pharmacotherapy is limited to metformin in some people (see **Chapter 9**) and structured educational support to begin and maintain meaningful weight loss and exercise levels remains the most effective intervention to reduce the risk of progression to diabetes.

It is also unhelpful to regard these biochemical states as static. For example, using continuous glucose monitoring techniques in people with definitely normal glucose status (low fasting glucose and strictly normal $HbA_{1c}$), three-quarters spent a median 30 minutes in each 24-hour period at glucose levels >7.8 mmol/l (140 mg/dl) and 7% had a peak glucose level diagnostic of diabetes (>11.1 mmol/l, 200 mg/dl) (Borg *et al*., 2010). Degrees of glucose tolerance are bound to change with changes in weight and exercise over a longer time-frame; these will, in part, account for advanced diabetic complications that are seen in some patients at the time of formal diagnosis. Careful consideration of overall cardiovascular risk factors and informed, focused discussion is the right approach.

**Practice point**

Prediabetes, defined as fasting glucose 5.6 (or 6.1) mmol/l to 6.9 mmol/l is best considered an indicator of other 'metabolic syndrome' characteristics, rather than a glucose value that exceeds an arbitrary level and therefore warrants 'treatment'.

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