INTRODUCTION

Diabetes mellitus (DM) is a group of heterogeneous disorders with distinct genetic, etiologic, and pathophysiologic mechanisms with the common elements of glucose intolerance and hyperglycemia, due to insulin deficiency, impaired insulin action, or both. The World Health Organization estimates that more than 220 million people worldwide have DM. The majority of these cases have type 2 DM. Currently, DM is classified on the basis of etiology and clinical presentation into four major types: 

(I) Type 1 DM: characterized by a gradual loss of insulin-producing β-cells, due to autoimmune destruction.

(II) Type 2 DM: caused predominantly by severe insulin resistance and subsequent β-cell failure.

(III) Gestational DM: defined as hyperglycemia with onset or first recognition during pregnancy.

(IV) Other Specific types: including monogenic forms of DM (neonatal DM and maturity onset diabetes of the young, or MODY), and DM that is attributable to
diseases of exocrine pancreas, other endocrinopathies, and drug-induced DM.

This overview will focus on the autoimmune type 1 DM; definition and criteria for diagnosis, epidemiology, pathophysiology, clinical presentation, management, comorbidities, and new developments in the treatment and prevention of type 1 DM.

DEFINITION

Type 1 DM results from deficiency of insulin secretion due to a gradual autoimmune, T-cell mediated destruction of the β-cells in people with genetic predisposition to this disease. Recently, more evidence has accumulated that B-cell autoimmunity also has a major role in the pathogenesis of type 1 DM. In 85–95% of cases of type 1 DM, at least one serum marker of autoimmunity is detected in the form of autoantibodies against insulin, islet cells, the protein tyrosine phosphatase IA2, the 65-kD form of glutamate decarboxylase (GAD-65), and the zinc transporter ZnT8. This subgroup of type 1 DM (with positive antibodies) is designated as type 1A, while the remaining 5–15% of cases of phenotypic type 1 DM but no detectable antibodies are referred to as “idiopathic” or type 1B. This does not necessarily mean that individuals with type 1B DM do not manifest markers of autoimmunity, but rather reflects our lack of knowledge of what these antibodies might be. Future discoveries of yet unidentified islet autoantigens may prove that in fact all cases of type 1 DM are autoimmune in nature. There have been limited efforts to further understand the pathophysiology behind this particular group of antibody-negative patients, with some data suggesting an increased incidence in individuals with African or Asian ancestry. This group tends to demonstrate a tendency for recurrent episodes of diabetic ketoacidosis (DKA) with varying degrees of insulin deficiency between episodes. This type of diabetes is strongly inherited and does not appear to have a genetic HLA-type association. There are also reports of a more fulminant form of β-cell destruction primarily in Japanese patients, with T-cell infiltration of the islets but no measurable autoantibodies.

Type 1 diabetes is generally thought of as “childhood or juvenile” diabetes, although it can be diagnosed at any age, with a peak incidence in the early teen years, around the time of puberty. Worldwide, the incidence of T1DM has been steadily increasing at an average annual rate of 3%.

EPIDEMIOLOGY

Worldwide, it is estimated that approximately 5.9%, or 246 million adults had diabetes in 2007. These estimates are expected to increase to some 380 million, or 7.1% of the adult population, by the year 2025. About 80% of these live in the developing countries where the largest increases will also take place.

In the United States, the National Diabetes Fact Sheet estimates that 23.6 million children and adults had diabetes in 2007, accounting for 7.8% of the population. Of those, around 5.7 million were undiagnosed, making DM one of the most prevalent chronic diseases that carries an economic burden of around US$174 billion per year. However, type 1 DM accounts for only 5–15% of these cases.

In the United States, approximately 30,000 new cases of type 1 DM are diagnosed each year; about two-thirds of them are in children under the age of 19 years.

PATHOPHYSIOLOGY

The autoimmune trigger in type 1 DM is the result of certain environmental exposures in genetically susceptible individuals. This genetic susceptibility is strongly linked to specific HLA genes which encode the major histocompatibility
complex (MHC) proteins. These proteins play a critical role in regulating immune responses and recognition of self vs non-self cells. Certain HLA types are associated with much higher risk for developing type 1 DM, with the HLA-DR3 and DR4, and HLA-DQ being the most common in people with type 1 DM, while other types (e.g., HLA-DR2) appear to be protective against developing autoimmunity against β-cells. The inheritance of particular HLA alleles can account for over half of the genetic risk for developing type 1 DM. Other genetic loci have been also identified.

While the genetics of type 1 DM continue to be carefully examined, identifying the environmental factors involved in developing type 1 DM remain largely uncertain. The increasing incidence of type 1 DM over the past few decades adds further evidence that environmental factors are of importance since it is not likely that genetic changes could take place in such a short period of time. Most of the findings in this field have been based on strong associations between the incidence of type 1 DM and certain environmental elements, but no definitive studies have clearly demonstrated a cause and effect with any of these factors. Examples of these associations have linked type 1 DM to dietary habits, vitamin deficiencies, exposure to certain viruses, and the so-called “hygiene hypothesis.” Population-based observational studies have found that children who were breastfed have a lower risk of type 1 DM than those who were not, and that exposure to cow’s milk before the age of 6 months doubles the risk of developing type 1 DM, particularly in individuals with high-risk HLA types. However, a recent report from Finland concluded that early exposure to cow’s milk is not a risk factor for developing type 1 DM. The EURODIAB Substudy-2 group suggested that rapid growth, rather than cow’s milk or early introduction of solid foods, may explain the increased risk for type 1 DM. Similar associations (although also controversial) have been found with intake of glutens, and foods rich in proteins, carbohydrates, and nitrosamine compounds.

In animals, a number of viruses can cause a diabetes-like syndrome. In humans, epidemics of mumps, rubella and coxsackie viral infections have been associated with increases in the incidence of type 1 DM. The viruses may act directly to destroy the β-cells, or by triggering a widespread immune response against several endocrine tissues including the β-cells. Some investigators postulate that this is an example of molecular mimicry between these viruses and the antigenic determinants on the surface of the β-cells. There is increasing evidence that inadequate vitamin D increases the risk for type 1 and type 2 DM, and other autoimmune conditions. This is supported by epidemiological findings of higher incidence of type 1 DM at higher latitudes and in other conditions with decreased sun exposure, and by the fact that vitamin D receptors are expressed in β-cells and in immune cells. Furthermore, certain polymorphisms within the vitamin D receptor gene are associated with development of type 1 DM, at least in some populations. In animal models, pharmacological doses of the active form, 1,25-dihydroxyvitamin D3, have been shown to modulate the immune system and delay the onset of diabetes.

The hygiene hypothesis suggests that avoidance to pathogen exposure secondary to improved living conditions leads to inadequate maturation of the immune system. The hypothesis is based on the increased incidence of diseases like asthma or other atopic disorders in children, in addition to the fact that type 1 DM is more prevalent in developed societies.

**DIAGNOSIS**

In general, DM is diagnosed when one or more of the following criteria are met:
1. Symptoms of diabetes plus casual plasma glucose concentration $\geq 200$ mg/dl (11.1 mmol/l); or
2. Fasting plasma glucose $\geq 126$ mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h; or
3. Two-hour post load glucose $\geq 200$ mg/dl (11.1 mmol/l) during an OGGT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g.

Recently, both the WHO and the American Diabetes Association have added the 4\textsuperscript{th} criterion of hemoglobin A1c $\geq 6.5\%$ as being diagnostic of DM.\textsuperscript{1}

As noted above, the presence of diabetes-related autoantibodies confirms the classification of type 1, while the presence of obesity, acanthosis nigricans, family history of type 2 DM, and other risk factors for insulin resistance such as the lack of physical activity or the ethnicity of Hispanic or African American origin, strongly point towards type 2 DM. However, type 1 DM can occur in obese individuals with one or more risk factors for insulin resistance, therefore screening for markers of autoimmunity is recommended in all cases of new onset DM.

**CLINICAL PRESENTATION**

Type 1 DM has four major clinical phases: preclinical diabetes, overt diabetes, partial remission phase (honeymoon), and the chronic phase.

In general, autoimmune destruction of the $\beta$-cells is a slow process that can take years before causing sufficient $\beta$-cell loss to cause insulin deficiency. Under normal physiological conditions, it is estimated that less than 50\% of the $\beta$-cell mass is sufficient to maintain euglycemia in humans. Typically, in individuals who are “developing” type 1 DM, a transient state of insulin resistance occurs, mostly due to a viral or bacterial illness, leading to increased requirements for insulin production which cannot be met because of the ongoing loss of $\beta$-cells. This leads to hyperglycemia, which itself has a detrimental effect on $\beta$-cell function leading to further hyperglycemia and its manifestations, leading eventually to the diagnosis of DM. It is estimated that only between 10\% and 40\% of the insulin-producing $\beta$-cells are still functioning by the time someone develops clinical manifestations of DM.\textsuperscript{63,64}

The symptoms and signs are related to the presence of hyperglycemia and the resulting effects of water and electrolyte imbalance. They generally include polyuria, polydipsia, polyphagia, weight loss and blurry vision. Onset of symptoms can be very variable from insidious to acute.\textsuperscript{65}

It is also not uncommon that new onset diabetes presents with a more serious and life-threatening diabetic ketoacidosis (DKA) with severe dehydration. The occurrence of DKA is more commonly seen in children younger than 4 years of age, and is less common in adolescents and young adults.\textsuperscript{64–66} Despite the increased awareness of diabetes in the public and among general practitioners, the incidence of initial DKA at diagnosis remains relatively high and varies between 15\% and 29\%.\textsuperscript{64–68} Typically the patient is acidotic with acetone fruity odor, respiratory distress, abdominal pain, nausea, vomiting, and polyuria and polydipsia. Laboratory findings include hyperglycemia, glucosuria, ketonemia, and ketonuria. Without timely management, severe fluid and electrolyte depletion develops with signs of hypoperfusion and altered mental status that may lead to coma and death.\textsuperscript{66,67}

Once the diagnosis is made, fluid resuscitation and insulin replacement can begin immediately. This reverses the metabolic derangements and hyperglycemia, which together with the recovery from the precipitating infectious process, leads to relative recovery of $\beta$-cell function and return to near-adequate insulin production to maintain euglycemia, heralding the honeymoon period.
This remission phase can last from a few months to 2 years in some cases. However, the process of β-cell destruction continues, eventually resulting in a gradual decrease in insulin secretion and ensuing hyperglycemia, marking the chronic phase of type 1 DM.

**MANAGEMENT**

The cornerstone of type 1 DM management is providing insulin at all times. This can be achieved by administration of one to two doses of long-acting insulin, and frequent prandial rapid-acting insulin. A series of modified human insulins with altered dynamics of absorption after subcutaneous injection have been introduced since 1996 and are now standard in clinical care including the long-acting insulins Glargine and Detemir, and the rapid-acting insulins Lispro, Aspart, and Glulisine. These “custom-designed” insulins provide excellent tools to try to mimic the physiologic patterns of endogenous insulin secretion and action, while minimizing the range of blood glucose excursions and the risk of hypoglycemia, two of the main obstacles to achieving more aggressive and optimal glucose control in patients with diabetes.

In most practices, newly diagnosed patients are started on multiple daily injection (MDI) of subcutaneous insulin, while those who present with DKA are treated initially with intravenous insulin infusion then switched to MDI. It is widely accepted that replacement of insulin in all patients with type 1 DM should consist of a combination of “basal and bolus” insulin. Typically, the dose of long-acting, basal insulin is unchanged from day to day and should provide about half of the total daily insulin requirements. However, the dosing of rapid-acting insulin is different for each time, and follows certain formulas to calculate the insulin dose for each meal based on the blood glucose (BG) value and the carbohydrate content in each meal (and snack). Alternatively, a continuous subcutaneous insulin infusion (CSII) pump is used to provide frequent small doses of rapid-acting insulin as basal insulin in lieu of the long-acting insulin, and user-administered boluses of rapid-acting insulin for meals and high BG. Because of this, management of type 1 DM requires self-monitoring of BG and a certain degree of competency in carbohydrate counting. Type 1 DM is recognized as a primarily self-managed disease, and to achieve the recommended glycemic targets patients need to receive ongoing nutritional counseling and training in self-management of their insulin regimen. In most practices, clinic visits with a team of physicians, diabetes educators, and nutritionists are recommended every 3-4 months.

In addition, a series of devices are now available for the continuous measurement of glucose concentration in the subcutaneous interstitial fluids, which reflects, with some time lag, the glucose concentration in the blood. These continuous glucose monitors (CGMs) can be operated alone or can be integrated with an insulin pump. The current devices provide predictive alarms for high and low BG, as well as continuous readings of glucose concentrations. Intense studies are ongoing for the development of the “closed loop” in which a CGM will control the operation of an insulin pump in response to changes in BG levels. Recent studies have shown improved glycemic control with the use of CGMs in type 1 DM. Using these tools, the goals of diabetes management in adults is to achieve a HgA1c of <7.0% with preprandial BG of 70–130 mg/dl (3.9–7.2 mmol/l) and a peak postprandial BG of <180 mg/dl (<10.0 mmol/l). These goals should be individualized in all patients and must be less stringent in children with type 1 DM.

**COMORBIDITIES**

The same genetic factors that pre-dispose patients to type 1 DM make them more likely
to develop other autoimmune diseases. The most common of these are thyroid autoimmunity, celiac disease, gastric autoimmunity, and Addison’s disease.

Autoimmune thyroid disease occurs in 17–30% of patients with type 1 DM. It is more common in females and is often associated with the presence of anti-thyroperoxidase (aTPO) and anti-thyroglobulin (aTG) antibodies. The current recommendations are for screening for aTPO and aTG at or shortly after diagnosis of type 1 DM, and measurement of TSH concentrations after metabolic control has been established. If normal, TSH should be re-checked every 1–2 years, or if the patient develops symptoms of thyroid dysfunction, thyromegaly, or an abnormal growth rate.

Celiac disease is an autoimmune enteropathy with a variable reported incidence of 1–10% in patients with type 1 DM, and is more common in children with the risk of developing celiac disease being about 10 times higher than the general population, especially in the first 5 years after diagnosis with type 1 DM. Celiac disease can manifest with non-gastroenterologic signs, including poor growth, delayed puberty, amenorrhea, erratic blood glucose concentrations, and even psychiatric problems. Therefore a high index of suspicion must be kept and periodic screening for serum levels of tissue transglutaminase (tTG) or anti-endomysial antibodies is recommended along with screening for thyroid disease in patients with type 1 DM. Some studies suggest that celiac disease is more likely to develop in the first 5 years after diagnosis of type 1 DM and is more likely in children diagnosed with type 1 DM before the age of 4 years than in those diagnosed as teenagers.

Also associated with type 1 DM is antigastric parietal cell and antiadrenal autoimmunity. These, however, are more rare than thyroid and celiac disease, such that routine screening is not currently recommended. However, because of the potential higher risk of developing pernicious anemia and gastric carcinoid tumors and adenocarcinomas, De Block et al. recently recommended periodic screening for antiparietal cell antibodies especially in adolescents with longer duration of diabetes, positive GAD-65 antibodies, and anti-TPO antibodies.

**COMPlications**

Chronic hyperglycemia and poor control of type 1 DM can lead to several long-term complications including hyperlipidemia, cardiovascular disease, peripheral neuropathy, and renal disease. These complications are similar to those seen in type 2 DM and are discussed in other chapters in this book.

**Prevention And Intervention Trials**

As mentioned earlier, the pathophysiology of type 1 DM encompasses several stages, beginning by activation of the immune system in genetically susceptible individuals, which leads to β-cell injury, impaired insulin secretion, and eventually frank hyperglycemia and clinical diabetes. This process is relatively slow and can take up to 2 years or more. By the time the diagnosis of type 1 DM is made, only 10–50% of islet cell mass remains intact but continues to be gradually destroyed over time. Therefore the principal challenge in any effort towards prevention of type 1 DM is the identification of at-risk individuals well before they lose a substantial β-cell mass. Currently, the best predictor of type 1 DM development is the presence of β-cell-directed autoantibodies, combined with carrying high-risk HLA alleles. In such individuals, several interventions have been tried, with little success in preventing the progression to overt diabetes. However, in the past few years, significant efforts have shifted towards strategies that aim at modulating the autoimmune response to
halt the destruction of pancreatic islets and preserving the remaining β-cells immediately after diagnosis of type 1 DM. Such strategies fall into two main categories: the first is antigen-specific, with interventions aimed at inducing tolerance to the specific antigen that is targeted, and the second is non-antigen specific, which aims to alter the function of components of the immune system, specifically T-cells and B-cells. Preliminary results have shown decreased insulin dependence at least in the first year after treatment and current extended phase 2 and 3 trials are being carried out. Once these studies have shown sufficient safety and efficacy in newly diagnosed patients, they will then be tested in at-risk individuals before they lose significant β-cell mass and become clinically hyperglycemic.

More recently, the role of vitamin D in regulating the immune system has gained much attention. A meta-analysis of recently published results suggested that vitamin D supplement given to children may reduce the risk for type 1 DM, particularly with doses of 2000 IU/day.

In the meantime, much effort is focusing on stem cell therapy by generating new β-cells from autologous umbilical cord blood cells and gene-engineered dendritic cells.

Other, more tertiary interventions such as whole-organ pancreatic transplant and transfer of isolated islet cells, combined with ongoing immune suppression, have both proven to be successful in terms of restoring glycemic level and insulin independence, but they remain limited by the availability of viable donor organ.

In parallel, there is continued strong interest in linking an insulin pump with a CGM to create an artificial pancreas.

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1. TYPE 1 DIABETES MELLITUS: AN OVERVIEW


I. EPIDEMIOLOGY AND OVERVIEW
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Overview of Type 2 Diabetes

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OUTLINE

Definition and Diagnostic Criteria 15  
Early Intervention in Type 2 Diabetes 21
Epidemiology of Type 2 Diabetes and Its Complications 17  
Clinical Management of Type 2 Diabetes 21  
Prevalence and Incidence 17  
Treatment Guidelines 21  
Complications 17  
Nutrition and Lifestyle Intervention 22  
Genetic Risk Factors for Type 2 Diabetes 18  
Pharmacological Treatments 22  
Risk Factors and Screening for Type 2 Diabetes 18  
Bariatric Surgery 23  
Diabetes in Pregnancy: Implications for Mother and Offspring 19  
Economic Impact of Type 2 Diabetes 23  
Evidence for Metabolic Programming of Diabetes in Early Life 20  
Future Directions 23

DEFINITION AND DIAGNOSTIC CRITERIA

A diagnosis of type 2 diabetes (T2DM) requires both biochemical criteria and etiological considerations. The World Health Organization (WHO) has recommended fasting and 2-h oral glucose tolerance tests (OGTT) for the diagnosis of T2DM (Table 2.1), and this classification of diabetes and impaired glucose regulation (IGR) is recognized by the American Diabetes Association (ADA). Although the ADA revised their...
diagnostic criteria in 2010, allowing the use of glycosylated hemoglobin (HbA1c) (Table 2.2), this suggestion remains controversial. An etiological classification of diabetes is described by the ADA, and is summarized in Table 2.3. The main problems with this classification are that many individuals with “T2DM” are atypical, and so etiology may be hard to determine. Some individuals with T2DM exhibit features such as ketosis or islet autoimmunity, which leads to confusion with type 1 diabetes (T1D). Moreover, whereas once most children diagnosed with diabetes were considered to have T1D, now up to 45% of new cases in some populations of children

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**TABLE 2.1** Values for Diagnosis of Diabetes and Other Categories of Hyperglycemia

<table>
<thead>
<tr>
<th>Glucose concentration, mmol.l⁻¹ (mgdl⁻¹)</th>
<th>Venous</th>
<th>Capillary</th>
<th>Plasma venous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting (or)</td>
<td>≥ 6.1 (≥ 110)</td>
<td>≥ 6.1 (≥ 110)</td>
<td>≥ 7.0 (≥ 126)</td>
</tr>
<tr>
<td>2-h post glucose load</td>
<td>≥ 10.0 (≥ 180)</td>
<td>≥ 11.1(≥ 200)</td>
<td>≥ 11.1(≥ 200)</td>
</tr>
<tr>
<td><strong>Impaired Glucose Tolerance (IGT):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting (if measured) and</td>
<td>&lt; 6.1 (&lt; 110) and</td>
<td>&lt; 6.1 (&lt; 110) and</td>
<td>&lt; 7.0 (&lt; 126) and</td>
</tr>
<tr>
<td>2-h post glucose load</td>
<td>≥ 6.7 (≥ 120)</td>
<td>≥ 7.8 (≥ 140)</td>
<td>≥ 7.8 (≥ 140)</td>
</tr>
<tr>
<td><strong>Impaired Fasting Glucose (IFG):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting and (if measured)</td>
<td>≥ 5.6 (≥ 100) and</td>
<td>≥ 5.6 (≥ 100) and</td>
<td>≥ 6.1 (≥ 110) and</td>
</tr>
<tr>
<td>2-h post glucose load</td>
<td>&lt; 6.1 (&lt; 110)</td>
<td>&lt; 6.1 (&lt; 110)</td>
<td>&lt; 7.0 (&lt; 126)</td>
</tr>
<tr>
<td></td>
<td>&lt; 6.7 (&lt; 120)</td>
<td>&lt; 7.8 (&lt; 140)</td>
<td>&lt; 7.8 (&lt; 140)</td>
</tr>
</tbody>
</table>

For epidemiological or population screening purposes, the fasting or 2-h value after 75 g oral glucose load may be used alone. For clinical purposes, the diagnosis of diabetes should always be confirmed by repeating the test on another day unless there is an unequivocal hyperglycemia with acute metabolic decompensation or obvious symptoms.


---

**TABLE 2.2** American Diabetes Association Diagnostic Criteria for Diabetes

<table>
<thead>
<tr>
<th>American diabetes association criteria for the diagnosis of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 HbA1c 6.5%. The test should be performed in a laboratory using</td>
</tr>
<tr>
<td>a method that is NGSP certified and standardized to the DCCT</td>
</tr>
<tr>
<td>assay.* OR</td>
</tr>
<tr>
<td>2 FPG 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric</td>
</tr>
<tr>
<td>intake for at least 8 h.* OR</td>
</tr>
<tr>
<td>3 Two-hour plasma glucose 200 mg/dl (11.1 mmol/l) during an Oral</td>
</tr>
<tr>
<td>Glucose Tolerance Test. The test should be performed as</td>
</tr>
<tr>
<td>described by the World Health Organization, using a glucose</td>
</tr>
<tr>
<td>load containing the equivalent of 75 g anhydrous glucose</td>
</tr>
<tr>
<td>dissolved in water.* OR</td>
</tr>
<tr>
<td>4 In a patient with classic symptoms of hyperglycemia or</td>
</tr>
<tr>
<td>hyperglycemic crisis, a random plasma glucose 200 mg/dl (11.1</td>
</tr>
<tr>
<td>mmol/l).</td>
</tr>
</tbody>
</table>

* In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

have T2DM, resulting in diagnostic uncertainty. The etiological diagnosis of T2DM also requires exclusion of other forms of diabetes, including monogenic forms. Therefore, whilst the classification is useful to assess new patients with diabetes, it does not provide a watertight definition of T2DM. The etiological classification could be improved with better recognition of the heterogeneity and polygenic nature of the disease.

### Epidemiology of Type 2 Diabetes and Its Complications

#### Prevalence and Incidence

More than 220 million people worldwide have diabetes and 80% live in low- to middle-income countries. The majority of these people have T2DM. In the US, 25.8 million people (8.3%) have diabetes, of which 90–95% have T2DM. Of these, 18.8 million (73%) are diagnosed and 7 million (27%) are undiagnosed. Amongst the >65 year age group, 10.9 million have diabetes, representing a prevalence of 26.9%. A further 50% of this age group (79 million) have prediabetes. Similarly, in the UK, where T2DM accounts for 92% of all registered diabetics, approximately 30% of people with diabetes remain undiagnosed in England and the actual prevalence was predicted to be 7.4% in 2010, rising to 8.5% by 2020 and 9.5% by 2030. By 2025, 300 million people worldwide will have diabetes. Thus, diabetes prevalence rates of 10–50% will be commonplace by 2030. Towards the end of the 20th century, especially high prevalences were observed in indigenous populations. Notably, in populations such as Native Americans, Pacific Islanders, and Aboriginal Australians, this high prevalence is linked to rapid transitions from traditional to modern lifestyles, major changes in diet and physical activity, and with excessive weight gain. Since much of that work, it has been apparent that the prevalence of diabetes is high and rising in most world populations. In China, the increasing affluence and changing lifestyles have seen dramatic increases in T2DM prevalence, particularly in urban populations. The numbers of adults with diabetes is projected to rise from 53.1 million in 2009 to 76.1 million in 2016. This represents a prevalence of 3.9% (urban 5.2%, rural 2.9%) in 2009, increasing to 5.4% (urban 6.9%, rural 3.8%) in 2016. In summary, T2DM poses a serious escalating public health problem, irrespective of gender, society, race, or age.

#### Complications

In 2005, there were 1.1 million deaths worldwide attributed to diabetes, almost half of which
were below the age of 70 years and 55% were women. It is predicted that worldwide diabetes deaths will double between 2005 and 2030.\textsuperscript{5} US data report diabetes as the seventh-highest leading cause of death, with heart disease listed as the highest and cerebrovascular disease as the third leading cause. However, only 35–40% of deceased people with diabetes have this condition listed on their death certificate. Furthermore, as a high percentage of diabetes remains undiagnosed, it is likely that diabetes as a cause of death is grossly underreported. Many of the cardiovascular deaths are likely to be associated with underlying diabetes.\textsuperscript{13} Similarly, macrovascular disease is the commonest cause of premature death in people with T2DM, and has been shown to reduce life expectancy of middle-aged males with T2DM in England by about 8 years.\textsuperscript{14,15} For individuals who develop uncomplicated T2DM in later life, there is likely to be less risk of progression of microvascular complications compared with individuals who develop this condition at a younger age, although risks vary between individuals. In general, younger patients with T2DM are likely to have high lifetime risks of both macrovascular and microvascular disease. A clear relationship between glycemic control and microvascular and macrovascular complications was shown in the UKPDS study.\textsuperscript{16} A 1% reduction in HbA1c was associated with 21% reduction in risk of any diabetes-related end point or death. Specifically, myocardial infarction risk is reduced by 14% and microvascular disease risk by 37% by reducing HbA1c from 7.9% to 7.0%. Long-term follow-up of patients with tighter glycemic control showed lasting reductions in macrovascular and microvascular disease.\textsuperscript{17} However, there has been controversy about tight glycemic targets. A meta-analysis of studies of intensive glycemic control suggested that risk reduction for major cardiovascular events was just 9%, accompanied by significant risk of hypoglycemia.\textsuperscript{18} Furthermore, there is evidence that lower levels of HbA1c are associated with increased mortality.\textsuperscript{19} Therefore, a current widespread view of glycemic control in T2DM is that this is best tailored to the individual. It has been suggested that younger patients with greater life expectancy merit more aggressive treatment than older patients with established cardiovascular complications and limited life expectancy.\textsuperscript{2}

**GENETIC RISK FACTORS FOR TYPE 2 DIABETES**

An early breakthrough in unravelling the complexity of T2DM came from the analysis of DNA from families with autosomal dominant diabetes, so-called Maturity Onset Diabetes of the Young (MODY).\textsuperscript{20} This family of disorders accounts for a few per cent of diabetes in some populations, and if not considered the diagnosis is missed.\textsuperscript{21} Nearly 30 susceptibility genes have now been identified, mainly influencing aspects of insulin secretion.\textsuperscript{22} Currently known genes appear to explain only a small fraction of inherited risk.\textsuperscript{23} While the mechanisms causing associations with T2DM remain unclear for most of these genes, the majority of the genes are expressed in islet \( \beta \)-cells. Thus, whilst obesity is an important cause of insulin resistance, and is a powerful risk factor for T2DM,\textsuperscript{24,25} genetic factors will protect some obese patients through \( \beta \)-cell compensation.

**RISK FACTORS AND SCREENING FOR TYPE 2 DIABETES**

The ADA\textsuperscript{2} advocates screening in high-risk, asymptomatic individuals, so that early diagnosis and treatment can prevent and delay complications. Common risk factors for T2DM and features to prompt screening are shown in Table 2.4. There remains controversy regarding the optimal testing strategy, and several tests are currently recognized. The two main tests

I. EPIDEMIOLOGY AND OVERVIEW
are fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) level after a 75 g OGTT. The adoption of HbA1c as a diagnostic test has been more controversial but was suggested by the ADA in 2010. No current screening or diagnostic test is completely interchangeable, since FPG and 2-h PG identify different individuals, many of whom are also missed with HbA1c. In women with polycystic ovary syndrome (PCOS) for example, the diagnosis of T2DM is usually missed with an FPG. The choice of test is also affected by whether the intention is to screen for IGR such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), which are currently essential if “prediabetes” is to be identified by blood glucose measures. HbA1c also fails to identify many individuals with IGR. Currently, screening has not been widely implemented in many risk groups, including those with obesity, women with PCOS or a history of gestational diabetes.

**DIABETES IN PREGNANCY: IMPLICATIONS FOR MOTHER AND OFFSPRING**

Gestational Diabetes Mellitus (GDM) has been widely defined as carbohydrate intolerance of variable severity with onset during pregnancy which returns to normal after delivery. Maternal hyperglycemia causes fetal hyperglycemia, fetal hyperinsulinemia and macrosomia, resulting in excess perinatal morbidity and mortality. Maternal risks include the need for induction of labor and caesarean section, and long-term risks of T2DM and possibly cardiovascular disease. The definition, diagnosis and importance of GDM have been controversial however. The Hyperglycemia and Adverse Pregnancy Outcomes Study (HAPO), found a clear association between maternal glucose levels below the threshold for diagnosis of diabetes and adverse outcomes in 25,000 pregnant women. In 2010, after years

**TABLE 2.4 Criteria for Diabetes Screening in Asymptomatic Adult Individuals at High Risk of Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Criteria</th>
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<tr>
<td>Overweight (BMI ≥ 25 kg/m² or lower in high-risk ethnic groups) or have additional risk factors:</td>
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<tr>
<td>Physical inactivity</td>
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<td>First degree relative with diabetes</td>
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<td>High-risk ethnic group</td>
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<tr>
<td>Women with previous GDM or macrosomic baby</td>
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<td>Blood pressure &gt; 140/90 or treated hypertension</td>
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<td>HDL cholesterol &lt; 35 mg/dl (0.9 mmol/l) and/or triglycerides &gt; 250 mg/dl (2.82 mmol/l)</td>
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<td>Women with polycystic ovary syndrome</td>
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<td>Previous IFG, IGT or HbA1c ≥ 5.7%</td>
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<tr>
<td>Other clinical condition associated with insulin resistance (e.g., acanthosis nigricans)</td>
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<td>History of cardiovascular disease</td>
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In the absence of the above criteria testing should begin at age 45 years.

If results are normal testing should be repeated at intervals of at least 3 years, with consideration of more frequent testing based on initial results and risk status.

of variation controversy, the International Association of Diabetes and Pregnancy Study Groups recommended the approach summarized in Table 2.5. These criteria recognize that standard criteria for the diagnosis of diabetes are inadequate for identifying levels of hyperglycemia (i.e., GDM) that affect the fetus. This study influenced the US change from screening based on GDM risk factors (such as BMI > 30, previous GDM, a previous macrosomic baby, diabetes in a first degree relative, or maternal origin from a high-risk ethnic group) to universal screening at 24–28 weeks’ gestation. However, the consequences of this are greatly increased screening of “low-risk” women.

Whether GDM requires active treatment was controversial for many years. The aim of treatment for women with GDM is to reduce maternal and neonatal morbidity with treatment options including diet and exercise, oral hypoglycemic agents and insulin. Recent studies show that pregnancy outcomes are improved by active treatment but that a high proportion of women with maternal hyperglycemia maintain good glycemic control without drug therapy. A recent systematic review and meta-analysis of major trials concluded that there were few differences in most outcomes when comparing metformin with insulin, but that metformin led to less maternal weight gain.

Maternal hyperglycemia has important long-term implications for both mother and child. The incidence of maternal T2DM after GDM is as high as 70% after 10 years. Finally, maternal GDM also results in increased long-term metabolic risk in their adolescent offspring. The consequences of GDM for the next generation are therefore an important emerging concern.

EVIDENCE FOR METABOLIC PROGRAMMING OF DIABETES IN EARLY LIFE

Neither traditional theories of genetic nor environmental causation account for increased risk of T2DM in adults who were of low birthweight for gestational age. Barker and Hales observed increased risks of IGT and T2DM in males who were of low birthweight. These and other findings led them to formulate the concept of the “thrifty phenotype” drawing on the earlier ideas of Neel. The hypothesis of “thrifty” metabolism postulates that evolutionary pressure from scarcity of food led to the selection of highly efficient insulin secretion and action and that fuel starvation during intrauterine life leads to adaptation to ensure survival but also results in permanent “programming” of metabolism. Neel proposed that this evolutionarily thrifty metabolism had
maladaptive consequences in the modern world, leading to T2DM. This concept is supported by experimental data showing that transient nutritional deficiencies in early life lead to permanent metabolic programming. The mechanism for programming of disease risk may involve inherited non-DNA, epigenetic modification through methylation and other chemical changes to DNA and histone proteins. If so, this could explain the well-known inter-ethnic differences in the risk of diabetes.

EARLY INTERVENTION IN TYPE 2 DIABETES

T2DM is often present years before diagnosis. Early diagnosis and treatment aim to reduce progression of cardiovascular disease and hyperglycemia. The need for targeted screening and early intervention in high-risk groups is not therefore in doubt. A range of drug-based interventions have demonstrated improved metabolic control and slower disease progression and data are emerging for the long-term effects of lifestyle intervention. Clearly, the earlier these interventions are instituted, the greater the potential reduction of long-term health risks. The risk of T2DM can be reduced substantially by weight reduction and drug interventions in high-risk individuals with IGT or obesity. These studies have provided a powerful impetus for diabetes prevention programs. However, it remains to be determined whether public health programs can afford to target the vast numbers who now meet criteria for diabetes screening, such as sedentary individuals with BMI > 25 kg/m².

CLINICAL MANAGEMENT OF TYPE 2 DIABETES

Key aims of T2DM clinical management are to reduce associated health risks, control symptoms and restore or maintain quality of life. This is achieved by a variety of interventions that include weight reduction through diet and exercise and using drug treatment to control risk factors for complications (i.e. levels of blood glucose, blood pressure and cholesterol). The underlying state of insulin resistance and insulin secretory failure provide the principles for these treatment options. Whilst the beneficial metabolic effects of weight loss are long established, it is comparatively recently that large-scale research into lifestyle and weight loss interventions has been taken seriously. Likewise, for selected patients with severe obesity, bariatric surgery offers a potential option. Other requirements considered necessary for effective T2DM treatment include patient education programs, a multidisciplinary team approach and regular recall for screening and monitoring. Favorable effects on quality of life and cost-effectiveness of care are also essential.

TREATMENT GUIDELINES

Medical treatment priorities are to achieve blood glucose levels as near to normal as possible and to lower cholesterol and blood pressure to reduce microvascular and macrovascular complications. The importance of tight glycemic control and treatment of hypertension is largely based on the findings of the UKPDS and post-trial follow-up. The ADA guidelines also include a significant focus on nutrition, exercise, weight loss and more recently the potential role of bariatric surgery in treating T2DM. In the wake of recent trials, however, there has been increasing recognition that targets for blood glucose lowering are best individualized, with less strict glycemic control being safer and more appropriate for older, frailer people with existing complications with relatively lower life expectancy. Based on some of these data,
along with recent safety concerns related to tight glycemic control,\textsuperscript{62} blood pressure and cholesterol targets will be the main focus of treatment for many.\textsuperscript{63}

**NUTRITION AND LIFESTYLE INTERVENTION**

Over the years, the importance of nutrition and lifestyle modification to treat T2DM has often been neglected. Increasing Body Mass Index (BMI) is associated with worse glycemic control and increased complications.\textsuperscript{64} However, definitive data are lacking and nutritional guidance and targets for physical activity have been controversial. The ADA clearly acknowledges the importance of nutrition and physical activity in the prevention and management of diabetes.\textsuperscript{27} This consensus statement highlights both nutrient-specific and obesity-related issues. The aim of modest weight loss is to improve glycemic control and reduce cardiovascular risk, based upon data from the Diabetes Prevention Program\textsuperscript{50} and the Look Ahead study.\textsuperscript{49} The ADA highlights the importance of reduced dietary fats, trans fatty acids and cholesterol. Furthermore, despite evidence of short-term weight loss and improved glycemic control with low-carbohydrate diets (<130 g/day carbohydrate), the long-term performance and safety of these diets have been controversial.\textsuperscript{27} Current ADA recommendations are to take at least 150 min/week of moderate-intensity aerobic physical activity, and unless contraindicated to perform resistance training three times per week.\textsuperscript{27}

**PHARMACOLOGICAL TREATMENTS**

The mainstays of treatment have traditionally been insulin, sulfonylureas and metformin. The impact of improved glycemic control using these three treatments was described by the UKPDS.\textsuperscript{59,60} The use of thiazolidinediones prompted treatment targeting insulin resistance. Pioglitazone was found to reduce macrovascular disease in high-risk patients,\textsuperscript{65} however cardiovascular concerns were encountered with other members of this class. The most recent additions to hypoglycemic drug therapies are Glucagon-Like-Peptide-1 (GLP-1) agonists\textsuperscript{66} and inhibitors of dipeptidyl peptidase-4 (DPP-4),\textsuperscript{67} both of which enhance insulin secretion. Whilst drug options for achieving glycemic control have broadened, the optimum order and combination of these treatments remains debatable.\textsuperscript{27} Latterly, tight glycemic control as the prime objective in treating T2DM has been questioned.\textsuperscript{18} The main comorbidity of T2DM is cardiovascular disease and therefore the treatment aim should be to reduce this risk. This is more readily achieved by treatments that target blood pressure and low-density lipoprotein (LDL) cholesterol.\textsuperscript{63}

Weight-loss drugs and weight-neutral hypoglycemic agents are a significant consideration, however no firm recommendation is yet possible without long-term data. Unfortunately, antiobesity drugs such as sibutramine and rimonabant have proven unsafe, although orlistat has demonstrated a modest effect on T2DM.\textsuperscript{68} Currently, GLP-1 agonists are promising for weight loss in T2DM.\textsuperscript{66} It appears appropriate therefore to consider these drugs in conjunction with active weight management programs such as that described in the Look Ahead study,\textsuperscript{49} although this remains to be explored. Whether the benefits of insulin, thiazolidinediones and sulfonylureas are offset by weight gain is unclear. The recognition of the benefits of weight loss in treating T2DM is an important factor in the mounting interest in bariatric surgery as a treatment for some patients. In summary, these trends indicate increasing acceptance of the significant need for targeting obesity in T2DM.
BARIATRIC SURGERY

Bariatric surgery came to prominence as a means to control T2DM in 199556 and has since attracted increasing attention.56 A range of surgical procedures is increasingly used to enhance the control of T2DM in obese individuals. The main operations currently used include roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB), biliopancreatic diversion (BPD), and recently sleeve gastrectomy (SG). These procedures appear to improve blood glucose levels through changes in gut hormones and afferent neural signalling. However, whilst these operations convey many benefits, their long-term role in treating T2DM has not been compared. A meta-analysis suggested T2DM “remission” in 78% of patients,70 with different rates with each procedure, although patient selection makes most of the patients unrepresentative of the general diabetic population.71 Another problem is the large number of uncontrolled retrospective studies. To date there has been only one small prospective randomized controlled trial comparing AGB versus medical treatment of T2DM, which achieved 72% normoglycemia 2 years after AGB vs 13% in the medical control arm.72 A subsequent analysis73 also suggested that AGB had a favorable health economic impact. However, diabetes relapse is also recognized after bariatric surgery.74,75 In addition to this, it is obvious that long-term treatments for diabetes should be safe. Whilst the short-term safety of bariatric surgery is well described76,77 more complex surgery leads to higher operative mortality and complication rates. Malabsorptive bariatric surgery also generates long-term micronutrient deficiencies that require close monitoring and replacement.78 There is currently increasing interest in using bariatric surgery as a diabetes treatment for people with BMI below 35 kg/m², although the ADA has urged caution and recommends further research.27

ECONOMIC IMPACT OF TYPE 2 DIABETES

At the beginning of the 21st century, T2DM is one of the most serious economic challenges facing the world. Reliable economic data are difficult to obtain, and so the best cost estimates come from more developed healthcare systems. In the US, for example, the total direct costs of treating diabetes were estimated at $116 billion in 2007, with an additional $58 billion in lost productivity,79 although these figures underestimated the full cost. Nevertheless, this still represented a colossal 12.8% of US Gross Domestic Product. Currently, T2DM poses the overwhelming economic burden, as a result of its prevalence and the costs of its complications.

In the UK, most routine management of diabetes is undertaken within primary care settings—91% of this is for T2DM. Between 1997 and 2007, prescribing costs for T2DM increased by 89%, with a 28% increase for diabetes-specific prescribing. There was a 112% increase in primary care appointments, and the overall costs of treating T2DM rose by 59%.80 Recent analyses have found 12.6% of acute hospital admissions to be diabetes-related, and that diabetes accounts for 10.8% of hospital outpatient attendances.81 The percentage of acute hospital expenditure attributable to diabetes rose from 8.7% to 12.3% between 1994 and 2004.81 Thus we have seen substantial rises in both primary and secondary care costs attributable to T2DM.

FUTURE DIRECTIONS

Diabetes researchers of the 19th and early 20th centuries would be amazed at the advances described in this book, although some fundamental controversies remain and new challenges have arisen. The major new challenge is the worldwide explosion of T2DM related to obesity. Although clinical trials have demonstrated the
feasibility of diabetes prevention,\textsuperscript{50,51,82} it has been less clear how to achieve this cost-effectively. Public health programs on this scale require political and economic cooperation. Weight loss is now commonly seen as a key treatment priority and yet many diabetes clinics remain poorly equipped to offer good support for weight loss. The optimum drug treatment regimens remain unclear with the use of oral agents, the newer incretin mimetics, and insulins requiring longer-term studies. Basic research on the molecular genetics and the endocrinology of T2DM and obesity—especially the mechanisms of diabetes remission after bariatric surgery—may lead to new forms of treatment.

References


I. EPIDEMIOLOGY AND OVERVIEW
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I. EPIDEMIOLOGY AND OVERVIEW
2. OVERVIEW OF TYPE 2 DIABETES


REFERENCES


