

# Type 1 diabetes

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Type 1 diabetes accounts for only about 5–10% of all cases of diabetes; however, its incidence continues to increase worldwide and it has serious short-term and long-term implications. The disorder has a strong genetic component, inherited mainly through the HLA complex, but the factors that trigger onset of clinical disease remain largely unknown. Management of type 1 diabetes is best undertaken in the context of a multidisciplinary health team and requires continuing attention to many aspects, including insulin administration, blood glucose monitoring, meal planning, and screening for comorbid conditions and diabetes-related complications. These complications consist of microvascular and macrovascular disease, which account for the major morbidity and mortality associated with type 1 diabetes. Newer treatment approaches have facilitated improved outcomes in terms of both glycaemic control and reduced risks for development of complications. Nonetheless, major challenges remain in the development of approaches to the prevention and management of type 1 diabetes and its complications.

In this age of increasing obesity, the epidemic of type 2 diabetes threatens both to overwhelm health care services and to obscure the health care implications and challenges of type 1 diabetes.<sup>1,2</sup> Although type 1 diabetes accounts for only 5–10% of all those with diabetes, it remains a serious chronic disorder, usually beginning earlier in life than type 2 diabetes, but with important short-term and long-term consequences.

In this seminar on type 1 diabetes I emphasise: (i) current theories of pathogenesis; (ii) epidemiology and presentation; (iii) management; (iv) diabetes-related complications; (v) psychosocial concomitants; and (vi) the challenges facing diabetes researchers and health-care professionals. Although not dealt with in this Seminar, issues such as diabetic ketoacidosis and its prevention and management, and the challenges of diabetes in pregnancy for both mother and fetus, should not be overlooked in the comprehensive care of individuals with type 1 diabetes.

## Pathogenesis

Type 1 diabetes is a condition in which pancreatic  $\beta$ -cell destruction usually leads to absolute insulin deficiency.<sup>3–6</sup> Two forms are identified: type 1A results from a cell-mediated autoimmune attack on  $\beta$  cells,<sup>4,6</sup> whereas type 1B is far less frequent, has no known cause, and occurs mostly in individuals of Asian or African descent, who have varying degrees of insulin deficiency between sporadic episodes of ketoacidosis.<sup>7</sup>

In the 1980s Eisenbarth<sup>8</sup> proposed the current model for the development of the immune form of type 1 diabetes and although our understanding has progressed significantly since then, the basic aspects of this model remain pertinent.<sup>4,6</sup> This model postulates that everyone is born with a degree of susceptibility to develop type 1 diabetes: for some this susceptibility is high, for others very low. Susceptibility is largely inherited, residing predominantly in the HLA genotypes DR and DQ, and to a lesser extent in a host of other genetic loci termed *IDDM* (insulin-dependent diabetes mellitus) susceptibility genes (table 1). The HLA locus is thought to confer about 50% of the genetic

susceptibility, roughly 15% from two other genes—*insulin-VNTR* (*IDDM2*) and *CTLA-4* (*IDDM12*)—with minor contributions from the other *IDDM* genes.<sup>4–6,9</sup> Both high risk (eg, *DR3/4*, *DQA1\*0301-DQB1\*0302*, and *DQA1\*0501-DQB1\*0201*) and protective HLA haplotypes (eg, *DQA1\*0102-DQB1\*0602*, associated with diabetes resistance, and DR molecules such as *DRB1\*1401*, associated with protection from diabetes) have been identified.<sup>4</sup> These susceptibility genes are thought to be important regulators of the immune response. Other genes associated with either rare syndromes including diabetes (eg, *AIRE* and *Foxp3*) or other autoimmune conditions (eg, *PTPN22*) might also provide important insights into the immune pathogenesis of type 1 diabetes.

The next step requires exposure to one or more environmental triggers that alter immune function, thereby initiating  $\beta$ -cell destruction. Putative triggers include viruses (eg, enteroviruses, coxsackie, congenital

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	Chromosome	Candidate genes/markers
IDDM1	6p21-31	HLA DR/DQ region Major role in presentation of peptides to T cells
IDDM2	11p15-5	Insulin-VNTR Protection associated with greater thymic insulin message
IDDM12	2q33	CTLA-4, CD28 Related to T-cell activation, thyroid autoimmunity

For many of those not listed (IDDM 3-11, 13-17), either the responsible gene remains unidentified or the gene function is uncertain in relation to type 1 diabetes.

**Table 1: Important susceptibility loci for type 1 diabetes**

## Search strategy and selection criteria

PubMed and the Cochrane Library database were searched with the terms: "type 1 diabetes", "insulin-dependent diabetes mellitus", "juvenile diabetes", "insulin" and "insulin analogues", "blood glucose monitoring", "glycosylated haemoglobin" or "haemoglobin A1c", "glycaemic index", "diabetes-related complications", "diabetic nephropathy", "retinopathy", "neuropathy"; and "macrovascular complications of diabetes". Most recent papers, systematic review articles, meta-analyses and evidence-based guidelines were preferentially selected.

rubella),<sup>10,11</sup> environmental toxins (eg, nitrosamines),<sup>12</sup> or foods (eg, early exposure to cow's milk proteins, cereals, or gluten).<sup>13–17</sup> A close relation has been identified only with congenital rubella.<sup>10,11</sup> The results of a 2004 study did not accord with a causal relation between childhood vaccination and type 1 diabetes.<sup>18,19</sup> Thus, the search for a so-called smoking gun trigger continues.

The abnormal activation of the T-cell-mediated immune system in susceptible individuals leads to an inflammatory response within the islets (insulinitis) as well as to a humoral (B cell) response with production of antibodies to  $\beta$ -cell antigens. Islet cell antibodies were the first described, but have been supplanted by more specific autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA/GAA), and the protein tyrosine phosphatase IA2 (IA-2AA), all of which are easily detected by sensitive radioimmunoassay.<sup>6</sup> The presence of one or more type of antibody can precede the clinical onset of type 1 diabetes by years or even decades. The presence and persistence of positivity to multiple antibodies increases the likelihood of progression to clinical disease.<sup>20–22</sup> There is no evidence that any of these antibodies has an active role in the pathogenesis of this disease in humans.

Continuing destruction of  $\beta$  cells leads to progressive loss of insulin-secretory reserve with, in order, loss of first phase insulin secretion in response to an intravenous glucose tolerance test, then to clinical diabetes when insulin secretion falls below a critical amount, and finally, in most but not all those with type 1 diabetes, to a state of absolute insulin deficiency.<sup>6,8</sup> The honeymoon or remission period takes place soon after clinical diagnosis and initiation of insulin therapy when some endogenous insulin secretion is restored to exhausted but not yet destroyed  $\beta$  cells, and when insulin resistance associated with initial hyperglycaemia is lessened.<sup>23,24</sup> In general, these cells are destroyed more rapidly when onset of clinical diabetes takes place at a young age, when there is also less likelihood of a long remission period.<sup>23</sup> Thus, older individuals are more likely to respond soon after diagnosis to immune interventions aimed at preserving residual insulin secretion.

Supportive evidence for the autoimmune pathogenesis of type 1 diabetes comes from the susceptibility of these individuals to other autoimmune conditions including Hashimoto's thyroiditis, Graves' disease, Addison's disease, coeliac disease, myasthenia gravis, and vitiligo.<sup>25–28</sup> Although recent knowledge has contributed to our understanding of the pathogenesis of type 1 diabetes, there remains no unifying theory of disease causation. The hygiene and accelerator hypotheses, however, warrant mention.<sup>29,30</sup>

The hygiene hypothesis stems from observations that atopic disorders such as asthma are more common in affluent than in traditional societies, their prevalence rising with increasing modernisation, and that such

disorders are less frequent in children in large families or those families receiving day care than in children in small families or those not in day care.<sup>29,31,32</sup> Similarities exist between these findings and reports of type 1 diabetes.<sup>33</sup> These findings suggest that children in these circumstances are less exposed to infections or other immune challenges early in life that act as protective environmental influences. Gale<sup>29</sup> has proposed that the protective effect is mediated by regulatory T lymphocytes. Although plausible, this hypothesis lacks credible scientific support in the causation of type 1 diabetes.

In the accelerator hypothesis, Wilkin<sup>30</sup> postulates that diabetes is a single disease, rather than two distinct entities, type 1 and type 2 diabetes. He argues that the two types of diabetes are distinguished only by the rate of  $\beta$ -cell loss, and the specific accelerators responsible. Wilkin implicates three accelerators: the first is the intrinsic potential for a high rate of  $\beta$ -cell apoptosis, an essential but insufficient step in the development of diabetes. The second accelerator is insulin resistance, resulting typically from weight gain and physical inactivity, and is central to the proposed link between the two types of diabetes. Insulin resistance puts pressure on a  $\beta$ -cell mass already at risk for accelerated apoptosis, contributing to the expression of clinical diabetes. The third accelerator is present only in those individuals with genetically determined predisposition to  $\beta$ -cell autoimmunity. The metabolically more active  $\beta$  cell, in insulin-resistant individuals who are genetically biased towards a high rate of apoptosis, is at greatest risk for rapid functional deterioration and expression of typical type 1 diabetes. In the absence of this immune accelerator, apoptosis is slower and progression is towards type 2 diabetes.

Proponents of the accelerator hypothesis claim that the rise in childhood obesity parallels the rise in both types of diabetes in childhood, and that the decreasing age of onset of type 1 diabetes in heavier children lends further support to their argument.<sup>34</sup> Opponents argue that there is sufficient evidence to support the Eisenbarth model for type 1 diabetes causation without having to implicate the other accelerators.<sup>35</sup>

## Epidemiology and presentation

Past descriptions depict type 1 diabetes as a disease of childhood and early adulthood, with a sudden, severe presentation—ie, most people being younger than 20 years of age at diagnosis and presenting in diabetic ketoacidosis. More recent data suggest that only about 50–60% of those with type 1 diabetes are younger than 16–18 years at presentation and that such disease occurs at a low incidence level throughout adulthood. Furthermore, studies of the natural history of type 1 diabetes in first-degree relatives with positive islet-related antibodies indicate that there is often a long prodrome preceding clinical onset, in which glucose homeostasis is either normal or only mildly disturbed.<sup>6,22</sup> Finally, diabetic ketoacidosis is not universal at disease

	Children	Adults	Comment
Duration of symptoms (weeks)	3–4	7–8	Large variability
Classic symptoms*	95%	96%	Rarely asymptomatic
Diabetic ketoacidosis at diabetes onset (%)	15–67%	~25%	
Age dependent:			
0–4 years	40–50%		The frequency of diabetic ketoacidosis at disease onset is inversely correlated with incidence in different geographical locations.
5–9 years	15–25%		
10–14 years	17–28%		
15–21 years	12–15%		

\*Polyuria, nocturia, enuresis, polydipsia, polyphagia, weight loss, lethargy, fatigue, abdominal pain. Data modified with permission from Booth<sup>38</sup> and Curtis and colleagues.<sup>39</sup>

**Table 2: Presentation of type 1 diabetes by age**

onset: in children, rates of 15–67% have been reported, inversely correlated with the incidence of type 1 diabetes in the particular geographic location.<sup>36,37</sup> Table 2 summarises the presentation of type 1 diabetes according to age.<sup>38,39</sup>

The epidemiology of type 1 diabetes has been reported in many countries, predominantly in children younger than 15–18 years of age. Many important observations derive from registries: first, incidence has been increasing at roughly 2–5% per year worldwide. The increase is steeper in the populations with a lower incidence; however, even in countries with the highest rates such as Finland, there has been no levelling off since statistics started being recorded in the 1950s.<sup>40–42</sup>

Second, there is huge geographical variation, with countries such as China reporting the lowest incidence rates (about 0.57 cases per 100 000 population younger than 18 years of age per year) to rates roughly 30 times higher in the UK (18–20 per 100 000 per year) to almost 100-fold higher (about 48–49 per 100 000 per year) in Finland and Sardinia.<sup>43–51</sup>

Third, there is a significant trend towards decreasing age at presentation, particularly in children younger than 5 years. The Swedish and Belgian data are notable here.<sup>52,53</sup> In Sweden from 1983 to 1998, the overall incidence of type 1 diabetes did not go up in the 0–34 year age group, but median age at diagnosis fell.<sup>52</sup> Similar findings were reported from 1989 to 2000 in Belgium in those younger than 40 years.<sup>53</sup> This shift to a younger age at diagnosis could indicate either exposure to heavier doses of environmental triggers or perhaps the increasing weight of the population.<sup>54,55</sup>

Finally, migrating populations take on the incidence rates of their new countries within a short time. For example, incidence rates for type 1 diabetes in south Asian children in the UK are similar to those of white or other ethnic backgrounds in the same area, which is in striking contrast to the very low rates reported from Asia.<sup>56</sup> This convergence of incidence rates for immigrant populations with those of the background population

lends support to a strong contribution of environmental factors in causation. This conclusion is further supported by reports that the rising incidence of childhood disease is associated with reduced contributions from high-risk HLA haplotypes.<sup>41</sup>

## Management

Intensive approaches to management are based on three sentinel observations highlighted by the extensively documented cohort of type 1 diabetes subjects enrolled in the Diabetes Control and Complications Trial (DCCT) and followed in the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.<sup>57–62</sup> First, the DCCT provided unquestionable evidence of a very close, curvilinear relation between the degree of glycaemic control (measured by haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) concentrations), maintained over the long term, and the onset or progression of microvascular (retinopathy, nephropathy, and neuropathy) and likely also macrovascular (cardiovascular, cerebrovascular, and peripheral vascular disease) complications.<sup>57,58</sup> Furthermore, there is no threshold effect: any decrease in HbA<sub>1c</sub> concentrations is associated with a similar decline in relative risk of complications. There is also no HbA<sub>1c</sub> level below which complications are completely prevented, nor one above which complications are certain to develop. These data underscore not only the pivotal role of glycaemic control, but also the presence of other factors, such as genes, smoking, obesity, hypertension, and hyperlipidaemia, in the development of complications.<sup>63</sup>

Second, the DCCT/EDIC cohort has convincingly shown that those initially treated intensively, and achieving reduced HbA<sub>1c</sub> concentrations, continue to have greater protection against development or progression of complications than those initially receiving conventional therapy.<sup>59–61</sup> This protection arises despite similar levels of glycaemic control in the 6–10 years after completion of the intervention part of the study. This metabolic or hyperglycaemic memory demands that intensive management be instituted as soon as diabetes is diagnosed.

Finally, there is an inverse relation between glycaemic control and the risk of severe hypoglycaemic episodes) in people with type 1 diabetes (panel 1).<sup>62</sup> In the DCCT, severe hypoglycaemia occurred about 2.5–3 times more often in those in the intensive therapy groups compared with those in conventional therapy groups; adolescents were about 1.5 times more likely to have hypoglycaemia than adults in both groups. In the youngest children with the disease, as well as in the older age group with enduring disease, repeated episodes of severe hypoglycaemia could lead to cognitive impairment.<sup>64–66</sup> Thus, hypoglycaemia is a major limiting step to achieving control with present treatment approaches. There are two caveats here: first, both in the DCCT<sup>62</sup> as well as in a study of almost 3000 children and adolescents

**Panel 1: Severity and treatment of hypoglycaemia**

- Mild: Autonomic symptoms (trembling, palpitations, sweating, anxiety, hunger, nausea, tingling) are present; can be self-treated with ingestion of simple sugars (10–15 g).
- Moderate: Autonomic and neuroglycopenic symptoms (difficulty concentrating, confusion, weakness, drowsiness, blurred vision, dizziness, difficulty speaking) symptoms are present, but the individual can still self-treat.
- Severe: Assistance of another individual is required to reverse hypoglycaemia, usually associated with confusion, convulsion or unconsciousness. Requires intravenous glucose (10–25 g) or subcutaneous glucagon (0.5–1.0 mg) injection.

with type 1 diabetes from 18 countries,<sup>67,68</sup> the risk of hypoglycaemia was not evenly spread across all centres compared with controls. Thus, some therapeutic approaches might foster glycaemic control without the same risk of severe hypoglycaemia. Second, treatments using insulin analogues or continuous subcutaneous insulin infusion pumps have a lower incidence of hypoglycaemia than seen with traditional insulins and delivery systems.<sup>69–74</sup>

Individuals should be fully informed about these rationales for management and provided with realistic targets for glycaemic control. Tables 3 and 4 provide glucose and HbA<sub>1c</sub> targets established in the evidence-based 2003 clinical practice guidelines of the Canadian Diabetes Association<sup>75</sup> for adults, children, and adolescents. Diabetes self-care requires a high standard of both initial and continuing education and care, best provided by a multidisciplinary health care team consisting of physicians, nurses, dietitians, and

	HbA <sub>1c</sub> (%)	FPG/preprandial PG (mmol/L)	2 h postprandial PG (mmol/L)
Targets for most patients	≤7.0	4.0–7.0	5.0–11.0
Normal range	≤6.0	4.0–6.0	5.0–8.0

Treatment targets must be tailored to the patient, with consideration given to individual risk factors. Normal range should be considered for patients in whom it can be achieved safely. HbA<sub>1c</sub>=haemoglobin A1c; FPG=fasting plasma glucose; PG=plasma glucose. Data used with permission from Canadian Diabetes Association.<sup>75</sup>

**Table 3: Glycaemia and HbA<sub>1c</sub> targets for adults with diabetes**

	Plasma glucose (mmol/L)	HbA <sub>1c</sub> (%)	Considerations
<5	6.0–12.0	≤9.0	Careful avoidance of hypoglycaemia in this age group due to risk of cognitive impairment
5–12	4.0–10.0	≤8.0	Adapt targets to patient's age
13–18	4.0–7.0	≤7.0	Appropriate for most patients
>18	4.0–6.0	<6.0	Only if targets can be achieved safely

HbA<sub>1c</sub>=haemoglobin A<sub>1c</sub>. Source: 2003 clinical practice guidelines of the Canadian Diabetes Association.<sup>75</sup>

**Table 4: Glycaemic and HbA<sub>1c</sub> targets by age for children and adolescents with type 1 diabetes**

**Panel 2: Components of management of individuals with type 1 diabetes**

- Appropriate insulin delivery: most regimens include either multiple daily injections or continuous subcutaneous insulin infusions with basal-bolus approach to insulin delivery
- Self-monitoring of blood glucose concentration: frequency of testing correlates with glycaemic outcomes
- Nutritional planning: more flexible programmes, including carbohydrate counting, replacing more rigid approaches
- Avoidance or treatment of severe hypoglycaemia and diabetic ketoacidosis: careful attention to other components of management greatly decreases risk of these short-term complications
- Screening for and treatment of associated disorders: specifically thyroid dysfunction (regular measurement of thyroid-stimulating hormone) and coeliac disease (specific antibodies—eg, tissue transglutaminase)
- Compensation for non-basal conditions—eg, physical activity, intercurrent illness, stress
- Screening for and treatment of diabetes-related complications.
  - Microvascular: retinopathy (eg, fundus photography), nephropathy (detection of microalbuminuria), neuropathy (clinical evaluation)
  - Macrovascular: detection of hyperlipidaemia and hypertension
- Attention to psychological and psychosocial wellbeing—eg, awareness of psychosocial stresses of chronic disorder; eating disorders; adolescent non-compliance; depression

behavioural specialists experienced in the management of type 1 diabetes.<sup>75–79</sup> Panel 2 shows the components of management.

Different centres use various approaches to insulin management, with increasing numbers of individuals using basal-bolus approaches with either multiple daily insulin injections or insulin pumps.<sup>80</sup> Table 5 details the characteristics of commonly used insulin preparations. Multiple daily injection routines have traditionally consisted of isophane (NPH) or ultralente given once or twice daily as the basal insulin, with regular human insulin boluses before meals. With the availability of both fast-acting and very long-acting insulin analogues, multiple daily injection routines increasingly use insulin glargine or detemir as the basal insulin and insulin lispro or aspart as the boluses before meals.<sup>69–74,81–83</sup> Insulin pumps use fast-acting insulin in a continuous basal rate with boluses before meals.<sup>84–87</sup> When basal-bolus routines are fastidiously applied in conjunction with the other aspects of management, many individuals with type 1 diabetes are able to maintain near-normal glycaemic control.

	Appearance	Action characteristics*		
		Onset	Peak	Duration
<b>Rapid-acting analogues</b>				
Insulin lispro	Clear	5–10 min	0.5–2	3–4
Insulin aspart				
<b>Fast-acting</b>				
Human regular insulin	Clear	0.5–1	2–5	6–8
Soluble insulin				
<b>Intermediate-acting</b>				
Isophane	Cloudy†	0.5–1	2–5	6–8
Lente				
<b>Long-acting</b>				
Ultralente	Cloudy†	3–4	8–15	22–26
<b>Very long-acting analogues</b>				
Detemir	Clear	0.5–1	None	20–24
Glargine				

This list represents the most commonly used insulin preparations and provides averages for the action characteristics, but these preparations also show variability within and between individuals. In general, there is less variability with insulin analogues than with either animal derived or biosynthetic human insulin preparations. \*Shown in hours, unless otherwise indicated. †Intermediate-acting and long-acting insulin preparations need agitation before use to allow resuspension, whereas very long-acting analogues do not.

**Table 5: Time course of action of currently available subcutaneously injected insulin preparations**

Both a meta-analysis and the Cochrane Metabolic and Endocrine Disorders Group reviewed randomised controlled trials comparing intensive therapy regimens using fast-acting insulin analogues with regimens using regular insulin.<sup>74,81</sup> A small ( $-0.1$  to  $-0.15\%$ ) but significant reduction in HbA<sub>1c</sub> was reported with the analogues, with comparable results between the analogues and regular insulin in terms of overall hypoglycaemia. Although fast-acting analogues did not notably reduce HbA<sub>1c</sub> levels, they might decrease macrovascular risk by reducing post-prandial glycaemia. Quality of life was improved with analogue use, largely because of the shorter interval between injection and food intake.

Several open-label randomised controlled trials as well as observational studies have assessed insulin glargine or detemir in adults with type 1 diabetes<sup>70–73,83</sup> All participants in these trials used basal-bolus insulin regimens. The results of most trials showed no differences in HbA<sub>1c</sub> concentrations between groups receiving insulin glargine or detemir, and those receiving isophane insulin. A few reported HbA<sub>1c</sub> decreases of 0.1–0.5% when insulin glargine was compared with isophane or ultralente. Some studies reported less night time or day time hypoglycaemia or less severe hypoglycaemic events in those receiving insulin glargine than in those receiving other types of insulin.<sup>73</sup>

Studies in children and adolescents with type 1 diabetes with insulin analogues show similar findings to those in adults.<sup>69,70</sup> Nonetheless, despite advances in insulin therapeutics during the past 25 years, only a few individuals with type 1 diabetes are able to reach the targets defined in tables 3 and 4.

Self-monitoring of blood glucose is fundamental to diabetes care.<sup>75,88,89</sup> Frequent monitoring facilitates improved glycaemic control, avoidance of hypoglycaemia, and lifestyle flexibility when the results are used to assist the individual in their dietary choices, physical activity, and insulin doses.<sup>90–92</sup>

Glucose monitors are now much smaller than previously, require very small amounts of blood (2–10  $\mu$ L), are faster at providing a result (5–15 s), and can be used at sites other than fingertips.<sup>89</sup> Verification of accuracy of self-monitoring is achieved by comparing results obtained from the patient's meter with a simultaneous specimen sent to the laboratory. A difference of less than 20% between meter and laboratory measurements is thought acceptable, which might be difficult in concentrations less than 4 mmol/L.

Most meters incorporate data management systems; however, keeping a blood glucose logbook is needed to detect patterns of glucose control and make appropriate dose adjustments. Continuous glucose monitoring technologies using subcutaneous sensors have become increasingly used in clinical care as a means of accessing more complete glycaemic data than is available with traditional self-monitoring.<sup>89,93</sup>

Whereas self-monitoring records daily variations in blood glucose concentrations, long-term control is best measured by HbA<sub>1c</sub> concentrations, indicating average glycaemic concentrations during the previous 90–120 days.<sup>94</sup> Each laboratory needs to standardise its HbA<sub>1c</sub> assay against either the DCCT or another internationally recognised reference laboratory since there are no universal standards against which individual assays can be calibrated.<sup>94–96</sup>

There are few data that lend support to rigid adherence to one particular approach to nutritional therapy in individuals with type 1 diabetes.<sup>97</sup> Thus, nutritional planning should be tailored to the individual's dietary preferences, age and stage of development, weight, culture, and lifestyle.<sup>97,98</sup> In general, patients are encouraged to follow guidelines for healthy eating similar to the general population—ie, varied consumption from all food groups, maintaining a healthy weight, limiting total fat to less than about 30% of daily caloric intake, and ensuring adequate intake of carbohydrate, protein, minerals, vitamins, and essential fatty acids. Consistency in meal planning can assist in reaching glycaemic targets, and modifications in the diet could also be helpful in achieving lipid and lipoprotein profiles aimed at reducing macrovascular risk. Nutritional planning in children and adolescents aims to provide adequate energy to promote normal growth and development.

Although most agree that the quantity of carbohydrate ingested substantially affects glycaemia, disagreement has focused on the importance of the quality of the ingested carbohydrate,<sup>98–100</sup> despite the demonstration of a five-fold difference in the effect on glycaemia when equivalent amounts of carbohydrate from different

sources are compared by glycaemic index. A meta-analysis of 14 randomised controlled trials (six in type 1 diabetes) shows a small but clinically significant improvement in HbA<sub>1c</sub> levels in those receiving low versus high glycaemic index diets.<sup>99</sup> Thus, individuals should be informed about the notion of glycaemic index and encouraged to incorporate foods that score lower on the index, such as wholegrain cereals, breads and pastas, fruits and vegetables.

Approaches with carbohydrate counting to the nutritional management of type 1 diabetes have developed in parallel with basal-bolus insulin regimens.<sup>98</sup> Carbohydrate counting allows adjustment of premeal insulin boluses of fast-acting insulin analogues according to both the premeal glucose concentration as well as the carbohydrate content of the meal. Calculation of insulin to carbohydrate ratios (ie, the amount of insulin needed to limit glycaemic excursions after meals) allows for increased flexibility in meal planning without sacrificing glycaemic control.

### Hypoglycaemia

Hypoglycaemia is a major obstacle to glycaemic control for many patients (panel 1). Causes include inadequate caloric intake, excessive insulin dosage, and inadequate preparation for physical activity. Often the cause cannot be determined.

Three issues are important: first, fear of hypoglycaemia often interferes with an individual's ability to achieve near-normal glycaemic concentrations.<sup>101</sup> This fear might be based on previous experiences with hypoglycaemia, or it may be part of wider anxiety about diabetes. Second, hypoglycaemia unawareness—ie, the occurrence of neuroglycopenia without early warning adrenergic symptoms, can occur in individuals with longstanding disease.<sup>102</sup> Finally, an episode of severe hypoglycaemia predisposes that individual to further episodes, as a result of downgraded regulatory responses to repeated hypoglycaemic events.<sup>103</sup> In these situations, reassessment of glycaemic targets is needed and the regimen adjusted to carefully avoid further episodes of hypoglycaemia.

Short-term risks of hypoglycaemia include potentially dangerous circumstances that may arise when someone is hypoglycaemic while, for example, driving a car.<sup>104,105</sup> Long-term consequences of severe, longstanding or repetitive hypoglycaemia include mild cognitive impairments in teenagers with early onset type 1 diabetes or older adults with longstanding disease.<sup>64–66</sup> Controversy remains about whether cognitive effects in young children are a result of severe hypoglycaemia or rather due to effect of chronic hyperglycaemia.<sup>106</sup>

Prevention of hypoglycaemia needs frequent blood glucose monitoring and careful balance between insulin dose, food ingestion, and physical activity. With respect to physical activity, the focus should be on adjustment of therapy to allow safe participation in these activities.<sup>107</sup>

### Panel 3: Risk factors for diabetes-related complications

- Poor glycaemic control
- Early onset and long duration of type 1 diabetes
- Genetic predisposition—eg, family history of diabetes-related complications or hypertension\*
- Smoking
- Obesity
- Sedentary lifestyle
- Hypertension
- Hyperlipidaemia

\*No single gene or cluster of genes has been identified that explains a major portion of the risk of microvascular or macrovascular complications. Candidate genes include those involved in the renin-angiotensin-system in nephropathy (eg, angiotensin-converting enzyme gene or angiotensin 2 receptor genes); genes related to disruptions in growth factors and cytokines (eg, vascular endothelial growth factor), the polyol pathway (eg, aldose reductase), protein kinase C activation, vascular or platelet function, or the nitric oxide pathway. So far, the demonstrated interactions between gene polymorphisms and diabetes-related complications have been quite weak.

Despite these efforts, severe hypoglycaemia occurs with a frequency of about five to 50 episodes per 100 patient-years, dependent both on treatment approach and level of control achieved.<sup>62,68</sup>

### Complications and comorbid conditions

Long-term diabetes-related complications are divided into microvascular and macrovascular disorders, which account for most of the increased morbidity and mortality associated with the disease (panel 3).

#### Microvascular complications

Diabetic nephropathy is the most common cause of renal failure in the developed world. The proportion of individuals who progress to end-stage renal disease used to be estimated as 30–40%; however, more recent data suggest that this proportion is decreasing, probably as a result of intensive efforts to control both glycaemia and hypertension.<sup>108–112</sup> In a cohort of 20 005 individuals from Finland diagnosed younger than 30 years of age between 1965 and 1999, Finne and colleagues<sup>111</sup> reported a cumulative prevalence of end-stage renal disease of 2·2% at 20 years and 7·7% at 30 years, which are much lower than previously estimated. Diabetic nephropathy progresses through a series of recognisable steps: from subclinical disease, to the earliest detectable phase of microalbuminuria (defined as a urinary albumin excretion rate >20<200 µg per day) to overt nephropathy or macroalbuminuria (>200 µg per day) with renal dysfunction and eventual end-stage renal disease.

The presence of microalbuminuria has been shown to be highly predictive of progression to advanced stages of diabetic nephropathy: a 75–80% probability of progression had been reported,<sup>108,109</sup> but more recently Perkins and colleagues<sup>110</sup> have suggested that the probability is only 50–66% and that, in a substantial

proportion, microalbuminuria can regress. These investigators showed that the factors predictive of greater likelihood of regression included younger age, improvement in metabolic control, reduced cholesterol and triglyceride concentrations, and lowered systolic blood pressure. In adolescents with microalbuminuria, progression is seen in about 50%, with regression in many of the others during 3–10 years' follow-up.<sup>63</sup>

Screening of individuals with type 1 diabetes for microalbuminuria should be instituted early in the course of their disorder: the Canadian Diabetes Association<sup>75</sup> suggests annual screening every year, with a random urine albumin-creatinine ratio in postpubertal individuals with diabetes of duration 5 years or greater. Positive screening tests should be confirmed with further random albumin-creatinine ratios or timed urine collections for 2–3 months. Persistent positive results require introduction of renoprotective measures, including further intensification of glycaemic control and control of hypertension or hyperlipidaemia, or both, if present.<sup>112,113</sup> First-line drugs of choice include angiotensin-converting enzyme inhibitors or angiotensin receptor-blocking agents, both of which are highly effective in slowing progression of renal disease in this population.<sup>113,114</sup>

Individuals who reach end-stage renal disease tend to do less well in dialysis and transplantation programmes than others with such disease that is unrelated to diabetes. The major part of the excessive cardiovascular morbidity and mortality resides in this group that develops advanced diabetic nephropathy.

Diabetic retinopathy is the most common cause of acquired blindness in the western world, with a prevalence rate of proliferative retinopathy of about 20–25% in type 1 diabetes.<sup>115</sup> It also progresses through recognisable stages: from early non-proliferative changes, previously called background retinopathy (microaneurysms, exudates, and haemorrhages), which appear in almost all individuals with type 1 diabetes by about 20 years' duration, to preproliferative retinopathy, and then predictably on to proliferative retinopathy (with risk of retinal detachment and vitreous haemorrhage) and macular oedema. Unlike early retinopathy, the later stages can be sight-threatening. There is a close association between diabetic retinopathy and diabetic nephropathy.<sup>116</sup>

Screening for diabetic retinopathy should begin 5 years after diagnosis in individuals of 15 years of age or older and be done yearly by one of the following methods: seven-field stereoscopic fundus photography interpreted by trained readers (gold standard); direct ophthalmoscopy or indirect slit lamp fundoscopy through a dilated pupil; or digital fundus photography.<sup>75</sup> The presence of diabetic retinopathy requires enhanced attention to glycaemic, blood pressure, and lipid control, with laser therapy in sight-threatening diabetic retinopathy.

Diabetic neuropathy refers to a complex group of conditions falling into two major categories: focal and generalised.<sup>117,118</sup> Focal neuropathies include, for example, carpal tunnel syndrome, peroneal nerve and third cranial nerve palsies, and diabetic amyotrophy (proximal nerve conditions). The most common generalised neuropathy is sensorimotor polyneuropathy, which often first presents as a peripheral neuropathy alone, but often also affects the autonomic system with cardiac dysfunction, gastroparesis, and erectile dysfunction. Peripheral neuropathy, in conjunction with peripheral vascular disease, can lead to skin ulceration of the lower limbs, poor healing and gangrene, and amputation (the diabetic foot). Good foot care may greatly lower the risk of these outcomes.<sup>75</sup>

Screening for neuropathy should also begin about 5 years after type 1 diabetes diagnosis, with appropriate methods: testing at the great toe with a 10 gauge monofilament to detect loss of sensitivity, and clinical assessment for the other manifestations.<sup>75</sup> Again, attention to glycaemic control represents the first step in management; if unsuccessful in controlling symptoms, referral to a specialist is indicated. Attention to preventive foot care is an essential component of diabetes management.

#### Macrovascular complications

Although cardiovascular disease accounts for about 70% of all deaths in people with type 2 diabetes, considerably less is known about its associations in type 1 diabetes. The relative risk of cardiovascular disease in type 1 diabetes can be as much as 10-fold greater than that in non-diabetic individuals. Risk factors for cardiovascular disease in type 1 diabetes include the presence of diabetic nephropathy, but also autonomic neuropathy, dyslipidaemia, hypertension, and perhaps also specific microvascular cardiac disease. The role of glycaemic control has not been easy to define, although two reports are important: a meta-analysis of randomised controlled trials in type 1 diabetes found that intensive insulin therapy may stabilise macrovascular disease or prevent progression in those at risk,<sup>119</sup> whereas the follow-up phase of the DCCT/EDIC showed that intensive treatment during the active intervention phase of the DCCT led to reduced progression of carotid intima-media thickness during 6 years' follow-up.<sup>120</sup>

Reduction of risk of vascular disease includes attention to healthy lifestyle (weight control and physical activity), smoking avoidance, with optimum glycaemic, blood pressure (<130/80 mmHg in adults), and lipid control (LDL-cholesterol <2.5 mmol/L and total:HDL-cholesterol ratios <4.0 mmol/L for those at high risk of an event, and <3.5 mmol/L and <5.0 mmol/L, respectively, for those at moderate risk<sup>75</sup>). There has been a steady decline in the recommended targets for lipid control with particular emphasis on control of LDL-cholesterol concentrations.

### Comorbid conditions

Clinical autoimmune thyroid disease occurs in about 5% and coeliac disease in 3–10% of children with type 1 diabetes.<sup>25–28</sup> The number of children with positive thyroid antibodies is higher than 5% (manifest disease) and increases with age. Annual screening of individuals with thyroid-stimulating hormone measurements will enable early initiation of thyroxine replacement therapy.<sup>26</sup> The need to screen for coeliac disease has been debated<sup>75</sup> but is now a recommended part of routine management.<sup>27,28</sup> The timing and frequency of screening for coeliac disease have not been defined; however, initial screening soon after diagnosis and then every 5 years is a reasonable recommendation. Although more common than in the general public, the presence of Addison's disease in individuals with type 1 diabetes is rare and screening cannot be justified.

### Psychosocial concomitants

Research has focused attention on the psychosocial concomitants of type 1 diabetes particularly in children and teenagers, but also in adults. For example, children from single parent families and low socioeconomic status are more likely to present in diabetic ketoacidosis at disease onset, have more episodes of diabetic ketoacidosis during the course of their diabetes, attend clinic less frequently, and are less likely to maintain good glycaemic control than those from two-parent and well-off families.<sup>121</sup> Furthermore, Kovacs and colleagues<sup>122</sup> showed that over 40% of teenagers had a period of pervasive non-compliance with major aspects of their diabetes routines, and that these individuals were more likely to show serious psychopathology—most commonly depression—in early adulthood.<sup>122</sup> Other researchers have also reported an increased prevalence of depression in adults with type 1 diabetes.<sup>123</sup>

Our research group has reported that nearly a quarter of teenage and young adult women with type 1 diabetes have either a full-blown (about 10%) or sub-threshold (about 14%) eating disorder, and that such disorders are associated with insulin omission to control weight through induced glycosuria, poor glycaemic control, and early onset of diabetes-related complications.<sup>124,125</sup> Interventions intended to improve the psychological concomitants of diabetes in an effort to enhance glycaemic control have not been very successful.<sup>126</sup>

### Challenges

Some of the challenges facing researchers and health-care professionals are as follows. First, we need to perfect the prediction model for type 1 diabetes in both high risk and general populations, and to develop effective and safe interventions that reverse the condition either in its preclinical or early clinical phase. The multicentre prevention trials (eg, European Nicotinamide Diabetes Intervention Trial of nicotinamide, and Diabetes Prevention Trial Type 1 of insulin), although ineffective,

have shown the usefulness of current prediction models and the feasibility of large-scale multinational studies.<sup>127,128</sup>

Second, techniques for islet cell replacement need to be improved, through either islet cell transplantation or islet differentiation from stem cell sources. Initial enthusiasm about improved outcomes of islet cell transplantation, raised by use of the Edmonton protocol<sup>129,130</sup> for islet harvesting and rejection prevention has been tempered by the lack of availability of islets, the side-effects of the procedure (such as bleeding, mouth ulcers, diarrhoea, anaemia, and ovarian cysts), and the increasing reversal of insulin independence in as many as 80% of the recipients 5 years after the transplantation, although some  $\beta$ -cell function and hypoglycaemia awareness seems to persist for longer than 5 years.<sup>129,130</sup> Stem cell research as a means of developing a potentially infinite source of functional islets is still at a very fundamental stage.<sup>131,132</sup>

Third, novel treatment strategies to achieve normoglycaemia are called for. Although insulin analogues and insulin pumps help more physiological insulin replacement approaches to be developed, they remain imperfect because of factors other than insulin that affect glycaemia (food intake, activity, stress, etc), the absence of closed loop systems linking insulin infusion to ambient glycaemia, and peripheral rather than portal insulin delivery. These shortcomings might be partly overcome by progress in development of continuous glucose monitoring systems. Linking of these systems to sophisticated pump technologies offers the promise of an artificial endocrine pancreas. Additionally, increasing rates of obesity have focused attention on the development of characteristics of type 2 diabetes in those with diagnosed type 1, so-called double diabetes (ie, increasing insulin resistance and cardiovascular risk).<sup>133</sup> This double diabetes has prompted the search for adjunctive drugs (eg, metformin) that might lessen the insulin resistance and improve glycaemic control.<sup>134,135</sup> Furthermore, drugs that either suppress glucagon (eg, amylin), or have multiple effects on pathways such as appetite regulation, stomach emptying, and continuing  $\beta$ -cell apoptosis, such as those with activity associated with glucagon-like peptide 1 (eg, exenatide and liraglutide), have potential to benefit individuals not only with type 2 diabetes, but also those with type 1 disease.<sup>136–138</sup>

Finally, we should define strategies for complication prevention or risk factors for development of complications. Better understanding of pathophysiological mechanisms and susceptibility genes is already leading to new targets for treatment.<sup>139</sup> In the meantime, attention should be focused on how to prevent complications with drugs such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), or even aspirin, deserves attention.<sup>140–142</sup> Evidence-based recommendations about the prophylactic use of these agents are not available.



## Conclusions

Type 1 diabetes has transformed from a disease with certain death in the era before the discovery of insulin to one with substantial risk of long-term morbidity and mortality.<sup>143</sup> For example, a report from the US Centers for Disease Control recently estimated that a 10-year-old boy or girl developing diabetes in the year 2000 would lose, on average, 18.7 and 19.0 life-years, respectively, compared with their non-diabetic peers.<sup>2</sup> Advances in treatment have resulted in improved outcomes, which come with increasingly complex and expensive therapeutic demands on individuals with type 1 diabetes.<sup>144–146</sup> Furthermore, Gale<sup>147</sup> has eloquently pointed out that, although focused studies show that outcomes can be improved by better management, there is “no evidence of this actually happening on a worldwide basis”.

A fundamental shift in the management of type 1 diabetes seems unlikely until we are able to close the loop through either artificial endocrine pancreas implantation, or islet replacement by transplantation or stem cell engineering. In the meantime, individuals with type 1 diabetes and their health providers need to focus their energies on the therapeutic approaches best capable of maximum risk reduction, including the risks of hypoglycaemia and diabetic ketoacidosis in the short term, and microvascular and macrovascular disease and psychological distress in the longer term.

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