Type 1 diabetes

*Teresa Quattrin*1,2,4, *Lucy D Mastrandrea*1,2,4, *Lucy S K Walker*3,4

**Affiliation:** Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo1, Diabetes Center, John R. Oishei Children's Hospital, Buffalo, New York, United States2, Institute of Immunity & Transplantation, Division of Infection and Immunity, University College of London, London, UK3 Full Professor 4

**Contributors:** All authors contributed to the manuscript conceptualisation, literature search, revisions, figures, and writing or editing of the paper.

**Declaration of interests:** TQ is a consultant for Jansen Research & Development, Merck, and Provention-Bio; a clinical site principal investigator (Buffalo, NY) for Janssen, Provention Bio, and TrialNet; and a sub-investigator for Novo Nordisk. LDM is a clinical site principal investigator (Buffalo, NY) for Novo Nordisk and JDRF, and a sub-investigator for Provention Bio and TrialNet. LDM is a member of the manuscript writing team for Novo Nordisk. LSKW received funding from the UK's Medical Research Council and Diabetes UK.

**Acknowledgments:** We acknowledge Paul Dressel for his expertise in medical illustration, and Mark Rigby and Joseph Hedrick for their contributions to the creation of figure 3. TQ received funding support from the National Center for Advancing Translational Sciences of the National Institutes of Health, under award number UL1TR001412 to the University at Buffalo. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. LSKW received funding from the Medical Research Council and Diabetes UK.

**Search strategy and selection criteria:** The strategy used for the Seminar was to search MEDLINE with the main search term, type 1 diabetes, alone and coupled with the key subsection headings (diagnosis, genetic and environmental contributions to type 1 diabetes, immunology of type 1 diabetes, role of the β cell in type 1 diabetes development, clinical management, preventing and treating type 1 diabetes complications, screening for risk of type 1 diabetes development, preventing or halting progression of β-cell demise, and biological treatment). Because the previous *Lancet* Seminar on the topic was published in 2018, the search was focused initially on publications between Jan 1, 2018, to Dec 31, 2022, and expanded retroactively when contributions to the literature were still relevant and pertinent to the current type 1 diabetes landscape. Only papers published in English were reviewed.

**Abstract**

Type 1 diabetes is a chronic disease caused by autoimmune destruction of pancreatic β cells. Individuals with type 1 diabetes are reliant on insulin for survival. Despite enhanced knowledge related to the pathophysiology of the disease, including interactions between genetic, immune, and environmental contributions, and major strides in treatment and management, disease burden remains high. Studies aimed at blocking the immune attack on β cells in people at risk or individuals with very early onset type 1 diabetes show promise in preserving endogenous insulin production. This Seminar will review the field of type 1 diabetes, highlighting recent progress within the past 5 years, challenges to clinical care, and future directions in research, including strategies to prevent, manage, and cure the disease.
Current landscape

The incidence of type 1 diabetes is not uniform worldwide. Type 1 diabetes is the third most common chronic disease of childhood, affecting one in 300 children, and there is consensus that the incidence is increasing.\(^1\) In the USA, epidemiological data on the incidence in adults are still scarce and suggest that 0·55% of adults in the USA have type 1 diabetes (based on self-reporting methods).\(^2\) There are wide discrepancies in age-standardised prevalence worldwide, ranging from 3·0/1000 people in Europe to 4·4/1000 people in North America, and from 0·6/1000 people in Asia to 0·8/1000 people in Africa.\(^3\) A meta-analysis (for publications between January, 1980, and September, 2019) reported the global incidence of type 1 diabetes to be 15/100 000 people and the prevalence to be 9·5/10 000 people.\(^4\) However, 3·7 million missing prevalent cases were estimated for 2021.\(^5\) The incidence of type 1 diabetes tends to be highest in higher income countries, where cases account for 49% of the worldwide incidence. This high incidence is partly due to increased recognition secondary to better access to health care.\(^3\) Although there have been notable advances in our understanding of the timeline to diagnosis, medical management, and prevention and treatment of complications, type 1 diabetes remains a disease with substantial burden for individuals affected and their caregivers. Moreover, data from the T1D Exchange are discouraging in that the advances have not been accompanied by improvement in metabolic control (figure 1).\(^6\) Even among adults, only 21% had glycated haemoglobin \(A_1C\) (HbA\(_1C\)) of less than 7·0% (53 mmol/mol). However, data from Belgium indicate that the control of type 1 diabetes could improve in a population receiving care from an integrated, nationwide, universal health-care system.\(^7\) Despite a decline in all-cause mortality in people with type 1 diabetes from Europe and the USA from 2000–16, this decrease does not compare favourably to improvements in mortality in populations without the condition.\(^8\)

Diagnosis

Although a diabetes diagnosis can be made on the basis of a fasting blood glucose concentration of 126 mg/dL or more, or on an abnormal blood glucose concentration during an oral glucose tolerance test, most individuals continue to be diagnosed on the basis of clinical criteria. These criteria include a random blood glucose concentration of 200 mg/dL or more, with classic symptoms of dysglycaemia, polyuria, polydipsia, and weight loss. In the absence of symptoms, confirmation of an abnormal blood glucose concentration (fasting, postprandial HbA\(_1C\)) is needed to establish the diagnosis. The incidence of type 1 diabetes increases during childhood and peaks between age 10 years and 14 years; however, diagnosis does occur in
adulthood, as data from the UK Biobank indicate that up to 40% of type 1 diabetes diagnoses occur after age 30 years.\textsuperscript{9} Children are more likely to present with diabetic ketoacidosis than are adults,\textsuperscript{10,11} and diabetic ketoacidosis at diagnosis is associated longitudinally with poorer diabetes control.\textsuperscript{12} The differential diagnosis between type 1 and type 2 diabetes can be challenging, particularly in adolescents and adults with obesity, who could be misclassified as having type 2 diabetes and be treated with oral medications.\textsuperscript{11,13} As type 1 diabetes treatment and prevention of complications improves, individuals diagnosed in childhood become adults with the condition; thus, prevalence is higher in adults than in youth.\textsuperscript{14} We refer readers to the 2021 comprehensive consensus report on the care of adults with type 1 diabetes.\textsuperscript{1}

**Genetic and environmental contributions to type 1 diabetes**

Type 1 diabetes is a complex autoimmune disorder with multiple factors implicated in its pathophysiology.\textsuperscript{15} Like other autoimmune diseases, its development involves genetic, immune, and environmental influences. A major component of the genetic risk maps to the human leukocyte antigen (HLA) complex; HLA-DR and HLA-DQ carry the strongest association.\textsuperscript{16} HLA molecules present antigens to T lymphocytes, highlighting their contribution to the disease pathogenesis. Besides the HLA region, more than 60 other loci are linked to type 1 diabetes. These loci include insulin gene polymorphisms that alter the amount of insulin mRNA presented in the thymus and possibly affect immune tolerance to insulin. Additional loci include genes involved in immune regulation such as *PTPN22, CTLA4, IL2RA,* and *PTPN2*.\textsuperscript{17,18} Many of these genes are associated with other autoimmune diseases such as autoimmune thyroiditis and rheumatoid arthritis, which co-occur with type 1 diabetes at rates greater than would be expected by chance.\textsuperscript{19} The strong genetic component of type 1 diabetes has led to the development of genetic risk scores on the basis of single-nucleotide polymorphism genotyping in both HLA and non-HLA regions. These scores accurately differentiate between people with type 1 diabetes, people with type 2 diabetes, and controls.\textsuperscript{20} Further information on how genetic variation influences the immunology of type 1 diabetes is provided in the next section.

Longitudinal studies have established that concordance of type 1 diabetes between monozygotic twins reaches 65% by age 60 years.\textsuperscript{21} The lack of complete concordance, along with rising incidence of the disease, highlights that environmental factors probably contribute to disease development. Environmental triggers linked to type 1 diabetes development include dietary factors, vitamin D status, obesity, and microbes as both infectious triggers and as gut microbiome
Enterovirus is the infectious trigger for which most supporting evidence exists, and prospective studies in children at high risk for type 1 diabetes identified a link between protracted enterovirus B infections and the development of pancreatic islet autoimmunity. Approaches are underway to test whether antiviral treatment in newly diagnosed individuals slows disease progression, and a coxsackievirus B vaccine is being developed with the aim of delaying or preventing diabetes.

**Immunology of type 1 diabetes**

An immune-driven cause is supported by the transfer of type 1 diabetes to an unaffected sibling after bone marrow transplantation and recurrence of the condition in recipients of pancreas–kidney transplants. In most cases, autoantibodies against β-cell antigens precede clinical type 1 diabetes by many years. Natural history studies evaluating individuals at high risk for developing type 1 diabetes elucidated the progression from serological autoimmunity (stage 1) to dysglycaemia (stage 2), and to clinical type 1 diabetes necessitating insulin therapy (stage 3). Individuals with a single islet autoantibody are at low risk of type 1 diabetes, whereas conversion to multiple islet autoantibody positivity clearly marks an increased risk of progression to stage 3. In mouse models, both CD4+ and CD8+ T cells are needed for diabetes development, and in people with type 1 diabetes, T cells specific for islet autoantigens are detected in the pancreas and pancreatic draining lymph nodes. As healthy individuals also have self-reactive T cells in their peripheral repertoire, the participation of these cells in β-cell destruction implies failure of immune regulation. Of note, interrupting immune regulation in patients with cancer with checkpoint inhibitor immunotherapy can trigger insulin-dependent diabetes, often with serological evidence of islet autoantibodies.

Regulatory T cells are important in immune regulation, and their role in controlling autoimmunity towards pancreatic islets is highlighted by the observation that type 1 diabetes with islet autoantibodies is a hallmark of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (or IPEX) syndrome, in which FOXP3 mutations render regulatory T cells defective. Despite broadly similar frequencies of regulatory T cells, there is evidence for their altered suppressive function in a subset of individuals with type 1 diabetes, and for reduced sensitivity of effector T cells to suppression, which is consistent with findings in mouse models. A major mechanism of regulatory T-cell function involves the inhibitory protein CTLA4; genetic variation at the CTLA4 locus and mutations in this gene are associated with type 1 diabetes risk. It has been suggested that...
HLA alleles associated with protection from diabetes might have a role in the selection of islet-specific regulatory T cells.51

Immune responses are multifactorial and involve the coordinated interaction of numerous cell types. In addition to B cells and T cells, roles for neutrophils, natural killer cells, macrophages, and dendritic cells have been suggested in type 1 diabetes.52–54 Cytokines released by immune cells are implicated in propagating the autoimmune destruction of β cells.55 There is evidence for a type 1 interferon signature preceding diagnosis,56 and neutralising self-reactive antibodies against type 1 interferons are associated with protection from type 1 diabetes in individuals with autoimmune regulator mutations.57

Insulitis (immune cell infiltration of islets) is a feature of type 1 diabetes58 but has proved challenging to study, partly due to the scarcity of biological material and because it dissipates once β cells are lost. In the non-obese diabetic mouse, there is evidence that tertiary lymphoid organs (TLOs; organised aggregates of T cells and B cells) form within the inflamed pancreas.59 These organs support local immune responses and can directly recruit lymphocytes from the circulation via specialised postcapillary venules. It was previously thought that these structures did not form in humans with type 1 diabetes; however, a 2021 analysis60 identified TLOs in pancreas samples from children with the condition. Diagnosis was earlier in children exhibiting TLOs (mean age 11·35 years [SD 6·59]) than in children without TLOs (mean age 16·74 years [4·76]). Additionally, TLOs were identified in a few individuals with stage 1 diabetes, suggesting their formation could precede clinical diagnosis.

The heterogeneity of type 1 diabetes with respect to age at diagnosis, disease severity, and pattern of insulitis gave rise to the concept of type 1 diabetes endotypes, which reflect underlying biological mechanisms.61 For example, the histological pattern observed in young children close to a diagnosis of type 1 diabetes shows more B cells and CD8 T cells than for children diagnosed after 13 years of age.62,63 This dichotomous pattern is associated with abnormalities in proinsulin processing, leading to elevated serum proinsulin to C-peptide ratios in children diagnosed before age 7 years versus children diagnosed after age 13 years.64

**Role of the β cell in type 1 diabetes development**

Increasing evidence supports a role for the β cell in the pathogenesis of type 1 diabetes. β cells are known to upregulate HLA molecules in individuals with type 1 diabetes, potentially attracting the attention of infiltrating T cells.65,66 The expression of HLA class II molecules on pancreatic β cells in type 1 diabetes has
been established, but this expression is modest, mainly cytoplasmic, and absent from autoantibody-positive individuals without diabetes.\textsuperscript{67} A 2021 analysis showed that pancreatic $\alpha$ cells express more HLA class I molecules than $\beta$ cells in the islets of both individuals with type 1 diabetes and autoantibody-positive donors.\textsuperscript{68}

Many genes associated with susceptibility to type 1 diabetes are expressed in $\beta$ cells, including $IFIH1$, $BACH2$, and $PTPN2$, which can modulate $\beta$-cell chemokine production and apoptosis.\textsuperscript{69–71} Pathway analysis of type 1 diabetes-associated genes that are expressed by $\beta$ cells suggests a key role for interferon-regulated pathways and the tyrosine kinase TYK2, which could have a role in RNA sensing following viral infection.\textsuperscript{72} The production of the T-cell chemoattractant CXCL10 by pancreatic $\beta$ cells\textsuperscript{73} in a TYK2-regulated manner\textsuperscript{72} emphasises the contribution of the $\beta$ cell in directing islet immune infiltration.

Two additional areas to consider from a $\beta$-cell centric view of type 1 diabetes pathogenesis are the role of endoplasmic reticulum stress and the generation of $\beta$-cell neoantigens. Endoplasmic reticulum stress, which results in an aberrant unfolded protein response, has been implicated in $\beta$-cell dysfunction in type 1 diabetes and could be triggered by viral infection, environmental toxins, or proinflammatory cytokines, such as interleukin (IL)-1$\beta$, TNF$\alpha$, and interferon-$\gamma$.\textsuperscript{74–76} One resident molecule in the endoplasmic reticulum implicated in the unfolded protein response is protein kinase-like ER kinase ($PERK$).\textsuperscript{77} $PERK$ gene mutations are linked to neonatal diabetes in humans.\textsuperscript{78} Cellular stress, inflammation, and reactive oxygen species stimulate post-translational protein modifications including deamination, oxidation, carbonylation, and citrullination. These modifications introduce neoantigens in the $\beta$ cell to which T cells are not tolerised. HLA class II molecules associated with type 1 diabetes show increased capacity to bind and present peptides that have undergone post-translational modifications,\textsuperscript{79} and these peptides are recognised by pancreas-infiltrating CD8$^+$ T cells in people with type 1 diabetes.\textsuperscript{80} An important class of modified antigens in type 1 diabetes are hybrid insulin peptides, which comprise a fragment of insulin covalently linked to other protein fragments.\textsuperscript{81} Hybrid insulin peptides have been identified by mass spectrometry in human pancreatic islets without type 1 diabetes, implying their presence alone is insufficient to cause diabetes.\textsuperscript{82} However, they have been validated as bona fide targets for the T-cell response in individuals with type 1 diabetes.\textsuperscript{36,83}

The cited studies raise the question of whether type 1 diabetes is driven primarily by an autoimmune response or by the $\beta$ cells themselves. Given the increasing appreciation of disease heterogeneity, we postulate that both are
required, with the relative contribution of each varying between individuals (figure 2). At the extreme ends of the spectrum, insulin deficiency could be almost entirely attributable to the immune system, as in the context of impaired immune regulation in patients with IPEX syndrome, or to the β cell, as seen in individuals exhibiting insulin misfolding\textsuperscript{84} or \textit{PERK} deficiency.\textsuperscript{78} However, in most cases, the situation will be more nuanced, with at-risk genes resulting in subtle changes in immune regulation or propensity for β-cell demise. The polygenic nature of type 1 diabetes highlights that immune or genetic inputs act collectively and occur against a background of environmental influences. Clearly, the environment can affect both the immune system and the target tissue; for example, viral infections have been shown to alter the autoimmune response via molecular mimicry,\textsuperscript{85} or via direct infection of the β cell.

\textbf{Clinical management}

\textbf{Insulin therapy}

The Diabetes Control and Complication Trial, and follow-up studies from cohorts enrolled in that study, showed that intensive diabetes management improved glycaemia and decreased the risk of diabetes complications, yet increased coincident risks of treatment-induced hypoglycaemia.\textsuperscript{86} Over time, exogenous insulin has evolved from animal-derived products to recombinant human insulin (regular insulin), administered with excipients to extend the glucodynamic properties (eg, neutral protamine Hagedorn and ultralente insulin), to recombinant insulin analogues designed to behave as rapid-acting or basal insulin. Most patients initiate multiple daily injection therapy to mimic endogenous insulin delivery. Here, a long-acting (basal) insulin analogue is given once per day, and a rapid-acting (bolus) insulin analogue is given by injection to account for carbohydrate intake or elevated blood glucose concentrations, or both.

However, when available, patients will use continuous subcutaneous insulin infusion (CSII; insulin pump therapy), which delivers flexible dosing of rapid-acting insulin to address circadian hormonal rhythms and individual insulin sensitivities related to food intake, stress, and exercise.\textsuperscript{87} CSII can deliver incremental insulin volumes as low as 0·025 U/h, allowing dose adjustments to suit even infants and toddlers with type 1 diabetes. Data from the T1D Exchange indicate that CSII use is widespread, although racial and ethnic disparities exist.\textsuperscript{88} The adoption of CSII is lowest in non-Hispanic Black populations (18\%) compared with non-Hispanic White (72\%) and Hispanic (40\%) populations.\textsuperscript{89}

Inhaled insulin exhibits a fast onset of action, allowing for a better match with the
postprandial glucose rise. Patients randomly assigned to Technosphere insulin (Technosphere, New York, NY, USA) versus analogue insulin achieved a similar time in range (time spent with a blood glucose concentration of 70–180 mg/dL),\(^90\) with less time spent in hypoglycaemia.\(^{91,92}\) A trial is ongoing in youth aged 4–17 years to assess the safety and pharmacokinetics in this younger population (NCT02527265).

**Continuous glucose monitoring (CGM) and goal HbA\(_1c\)**

CGM reports interstitial blood glucose concentrations as a surrogate for capillary glucose, providing real-time data and glycaemic trends.\(^93\) This tool allows for an increase or decrease in insulin administration if blood glucose concentrations are rising or are predicted to fall into the hypoglycaemic range. Historically, optimising glycaemic control has been linked to HbA\(_1c\) concentrations, with international societies recommending optimal glycaemic targets of less than 7% (53 mmol/mol) for all ages.\(^94\) However, these HbA\(_1c\) targets might not be relevant for all patient populations (table) and can be personalised on the basis of an individual’s risk of hypoglycaemia and access to advanced technologies.\(^94\) In addition, glycaemic variability is associated with poor diabetes outcomes such as an increased risk of hypoglycaemia and long-term diabetes complications.\(^96\) CGM data can be used to measure time in range.\(^90\) Sensor-augmented pump therapy pairs CSII with CGM to adjust basal insulin delivery on the basis of the predicted sensor glucose concentration, with some algorithms providing automatic correction boluses in case of predicted glycaemic concentrations that are above target. Conversely, the system decreases basal insulin delivery and warns the person if their blood glucose concentration is trending towards hypoglycaemia. The user must still inject a bolus dose for carbohydrate intake and elevated blood glucose concentrations. In a further technological advancement known as the bionic pancreas, algorithms integrating insulin pump therapy with CGM that require only the announcement of meals, rather than user-initiated carbohydrate bolusing, showed improvement in HbA\(_1c\) compared with standard care (ie, any insulin delivery in addition to CGM).\(^97\) These systems can decrease the overall burden of diabetes management and increase a person’s time in range.\(^98,99\)

CGM can improve glycaemia and communication between patients and healthcare providers.\(^100–102\) Smartphone applications have been developed to improve self-management of blood glucose concentrations,\(^103\) resulting in improved metabolic control and decreased hypoglycaemia in users,\(^104\) and reduced caregiver fear of hypoglycaemia.\(^105\)
**Dietary management**

Nutrition is an essential component of diabetes management and should be reviewed at least once per year depending on the person’s diabetes control and weight status. Although both fat and protein contribute to postprandial glucose excursions, most patients rely on carbohydrate-based insulin dosing. Dietary counselling needs to be culturally sensitive and tailored to individual food preferences, with specific education on glycaemic index and food quality. Current recommendations indicate that approximately 50% of adults’ and children’s daily caloric intake should come from carbohydrates. In adults, very low carbohydrate diets have been associated with lower HbA1c and triglyceride concentrations, and reduced insulin requirements. However, the effect on HbA1c is variable in adults who restrict carbohydrates to less than 45% of their dietary intake, with some studies showing no changes and some showing significant reductions in HbA1c. A 2021 report compared 36 children (median age 11·9 years) who followed a low carbohydrate diet (where daily energy intake from carbohydrates is less than 26% of age-recommended values) with 36 controls matched for age, type 1 diabetes duration, and age of onset. An increased time in range, with more time in hypoglycaemia, was observed in the low carbohydrate group compared with controls. HbA1c or BMI did not differ between the groups. Further prospective studies are needed to establish the efficacy and safety of a low carbohydrate diet, particularly in youth, whose growth can be affected by carbohydrate restriction.

**Obesity in type 1 diabetes**

An often overlooked issue in the management of type 1 diabetes is the increasing prevalence of obesity (12·0–52·4% in adults). In a historical cohort of people diagnosed with type 1 diabetes who were followed up for 18 years, the prevalence of overweight increased by 47% and obesity by seven-fold compared with baseline. Importantly, subcutaneous insulin delivery does not restore intraportal insulin-like growth factor 1 concentrations, contributing to increased serum concentrations of growth hormone and further worsening obesity-related insulin resistance. A 2017 survey showed that more than a third of adolescents with type 1 diabetes are overweight or obese, with the highest rate of obesity in female participants and minority ethnic individuals. Besides causing poor mental health outcomes and being a risk factor for stroke and cancer, obesity increases the risk of hypertension and dyslipidaemia, both of which are precursors of diabetes-related vascular disease. In view of this clinical reality, several drugs approved for type 2 diabetes have been studied as repurposed adjunctive therapy. Although not statistically significant, insulin doses decreased and lipid panels improved in adult
and adolescent cohorts treated with metformin, but glycaemic control was similar.\textsuperscript{115,116} Clinical trials with GLP-1 receptor agonists showed modest improvements in HbA\textsubscript{1c} with a coincident decrease in total daily insulin dose and bodyweight;\textsuperscript{117} however, this drug class is not licensed for use in individuals with type 1 diabetes.\textsuperscript{118} In adult studies, adding either sodium-glucose cotransporter 2 or SGLT1 or SGLT2 inhibitors showed some improvement in glycaemic control, but had the risk for euglycaemic diabetic ketoacidosis.\textsuperscript{119,120} The only drug currently approved as adjunctive therapy for type 1 diabetes is pramlintide, an analogue to amylin (a peptide secreted with insulin by \( \beta \) cells).\textsuperscript{121} This drug is co-administered with insulin at meals, and individuals should decrease their insulin dose to minimise hypoglycaemia risk. Less than 5\% of individuals with type 1 diabetes are treated with approved and unlicensed adjunctive therapies.\textsuperscript{122}

**Mental health**

The burden imposed on people with type 1 diabetes is often associated with mental health issues such as anxiety and depression, with depression being three times higher in people with type 1 diabetes than in the general population.\textsuperscript{123} Individuals with comorbid mental health concerns have less participation in self-care behaviours and a diminished quality of life.\textsuperscript{124} Mental health screening should therefore be part of routine health care for people with type 1 diabetes.\textsuperscript{125}

**Smoking and vaping**

Data from the Diabetes Control and Complication Trial showed that smokers with type 1 diabetes were at an increased risk of developing retinopathy (43\%) and renal disease (36\%) compared with non-smokers,\textsuperscript{126} and smoking increases lipid concentrations, therefore contributing to dyslipidaemia. Tobacco use among 13–15-year-olds is alarmingly high worldwide.\textsuperscript{127} In North America, 1.3\% of middle school students and 3.8\% of high school students reported current use of two or more tobacco products, and 11.3\% reported use of electronic cigarettes.\textsuperscript{128} Tobacco use is a leading cause of cardiovascular disease, and smoking represents a modifiable risk factor for people with type 1 diabetes. Due to challenges eliciting a smoking history in the health-care setting, providers should counsel their patients with type 1 diabetes irrespective of endorsed smoking history.

**Bone health**

In 2021, a large meta-analysis concluded that bone development, as measured
by multiple methods, is atypical in people younger than 20 years with type 1 diabetes.\textsuperscript{129} We reported that bone mineral density was lower in women aged 13–35 years than in controls; a difference that persisted in a 2-year follow-up study.\textsuperscript{130} This problem worsens with age as premenopausal women with type 1 diabetes have reduced bone mineral density and calcaneal quantitative ultrasound compared with controls.\textsuperscript{131} Observational studies have reported the association of type 1 diabetes with increased risk of fractures compared with controls, with a seven-fold increase in hip fractures.\textsuperscript{132} Given the early onset of low bone mineral density leading to future bone fragility, and the availability of approved therapies, we suggest that bone mineral density assessment should be part of routine care in young adults with type 1 diabetes, particularly in women.\textsuperscript{133}

**Preventing and treating type 1 diabetes complications**

Hypoglycaemia remains one of the most frightening risks in the lives of individuals with type 1 diabetes. The American Diabetes Association classifies hypoglycaemia severity as level 1 with a blood glucose concentration between 54 mg/dL and 70 mg/dL, level 2 with glucose less than 54 mg/dL, and level 3 as any event “characterised by altered mental and/or physical status requiring assistance for treatment”.\textsuperscript{134} Level 2 events particularly affect activities of daily living and can affect cognitive function.\textsuperscript{135,136} In response to fear of hypoglycaemia, patients’ and parents’ compensatory behaviours can lead to permissive hyperglycaemia with poorer metabolic control.\textsuperscript{137} In 5–9-year-olds with recent onset type 1 diabetes, CGM led to a reduction in hypoglycaemia-avoidance behaviours in parents.\textsuperscript{138} However, studies examining the effect of CGM on severe hypoglycaemia in adults and youth have not had uniform results.\textsuperscript{139,140} In adults on multiple daily injection regimens with histories of hypoglycaemia unawareness or severe hypoglycaemia, CGM led to a reduction in hypoglycaemic events from 10·8 to 3·5 per 28 days, compared with no changes in controls.\textsuperscript{141} In adults older than 60 years, CGM use led to a decline in time in hypoglycaemic range from 73 min to 39 min per day, but this remained unchanged in the group using meter testing.\textsuperscript{142} Although most participants did not achieve the primary aim of spending less than 1% of time in the hypoglycaemic range, the potential for CGM to decrease the rate of mild hypoglycaemia is clinically relevant because recurrent mild hypoglycaemia is implicated in the genesis of hypoglycaemia unawareness.\textsuperscript{143}

Glucagon is the mainstay rescue therapy for level 3 hypoglycaemia. Previously, glucagon was only available as a lyophilised powder requiring reconstitution and intramuscular administration, but new glucagon formulations obviate the need for glucagon preparation during a stressful clinical scenario.
Nasal glucagon is a powdered formulation approved as a single-dose rescue treatment for severe hypoglycaemia.\textsuperscript{144,145} Soluble recombinant human glucagon is available in two fixed-dose (weight-based) auto-injector pens or as a vial and syringe kit to be administered subcutaneously.\textsuperscript{146} Dasiglucagon has improved stability secondary to seven amino acid changes compared with native glucagon, and is administered subcutaneously with a prefilled syringe or single-dose auto injector.\textsuperscript{147} Soluble glucagon formulations could be included in dual-hormone, sensor-augmented pump systems\textsuperscript{148} to decrease hypoglycaemia risk as glycaemic concentrations improve.

Diabetic ketoacidosis is a metabolic emergency commonly associated with new diagnoses of type 1 diabetes but can also occur in people with a longstanding diagnosis, particularly in adolescent girls and individuals with a previous history of the condition. Diabetic ketoacidosis at diagnosis was found to have increased from 41\% in 2010, to 58\% in 2017, in youth followed up at the Barbara Davis Center (Aurora, CO, USA).\textsuperscript{149} The condition is associated longitudinally with poorer diabetes control than in people who did not present in diabetic ketoacidosis,\textsuperscript{12} and is more prevalent in younger children, people without a family history of type 1 diabetes, and people with lower socioeconomic status.\textsuperscript{150} During the COVID-19 pandemic, individuals with new onset type 1 diabetes were more likely to present in diabetic ketoacidosis despite being COVID negative at the time of diagnosis.\textsuperscript{151,152} Unsurprisingly, intensive monitoring of children with genetic risk for type 1 diabetes from 3 months old resulted in lower diabetic ketoacidosis rates than for other similar registries.\textsuperscript{153}

**Type 1 diabetes-associated comorbidities**

Although optimising glycaemic control is essential for preventing progression of microvascular and macro-vascular disease in people with type 1 diabetes, as more patients enter later decades of life, attention should be placed on diagnosing and managing comorbidities. We have summarised the current recommendations for screening and treatment (table);\textsuperscript{154} risk score calculators are also available to guide treatment.\textsuperscript{155}

Dysglycaemia is a strong contributor to vascular disease and its associated complications. Hypertension and dyslipidaemia, risk factors for macrovascular disease, are prevalent in the general population and are exacerbated by poor blood sugar control. Almost 10\% of patients with type 1 diabetes have normal blood pressure in a doctor’s office but can have abnormal readings at other times. Conversely, 32\% of patients could have white coat hypertension.\textsuperscript{156} This finding highlights the importance of assessing blood pressure in alternate settings such
as a school nurse or physician’s office. In some cases, ambulatory blood pressure monitoring can be considered, especially when deciding if and when to initiate treatment with antihypertensive therapy. Maintaining healthy weight, with attention to nutrition and exercise, is essential for managing both hypertension and dyslipidaemia. Unfortunately, however, these preventative strategies are difficult to implement, especially if healthier habits are not pursued by the extended household or family.

**Microvascular complications**

Prevention of nephropathy, retinopathy, and neuropathy is dependent on optimal metabolic control. Screening for early signs of microvascular disease positively alters progression of complications. In a study of adolescents with type 1 diabetes with albumin-to-creatinine ratios in the upper third of the population, treatment with either an angiotensin-converting enzyme (ACE) inhibitor or statin, or both in combination, did not improve albumin excretion. However, ACE inhibitors decreased the incidence of microalbuminuria compared with the placebo group, and statins reduced total amounts of low-density lipoprotein and non-high-density lipoprotein cholesterol significantly.

**Autoimmune disease**

Clinicians should be aware that additional autoimmune disorders present with higher frequency in individuals with type 1 diabetes. The most common disorders include autoimmune thyroid disease (either hypothyroidism or hyperthyroidism), coeliac disease, and primary adrenal insufficiency. Screening for thyroid and coeliac disease should occur annually or when clinical symptoms arise, and evaluation for cortisol deficiency when a patient has unexplained hypoglycaemia, electrolyte disturbances, or impaired growth. Other conditions, although less common, need to be considered on the basis of signs or symptoms such as pernicious anaemia, hypogonadism, and juvenile idiopathic arthritis.

**Screening for risk of type 1 diabetes development**

The risk for autoimmunity and type 1 diabetes is ten-fold higher in youth with a first-degree relative with the disease than in the general population. The TrialNet Consortium has screened first-degree relatives since 2001 and has delineated the natural history of type 1 diabetes. Specific high-risk HLA haplotypes have been identified and the timing of pancreatic autoantibody appearance, and the significance of multiple antibodies with respect to type 1 diabetes onset, has been elucidated. Screening this cohort has allowed for the development of clinical trials that aim to delay the progression from autoimmunity (stage 1) to dysglycaemia.
(stage 2), and to clinical diabetes, for which insulin therapy is required. Only very few participants without a family history of type 1 diabetes entered the TrialNet Pathway to Prevention (or TN01) because they were found to be positive for autoantibodies. Moreover, most individuals (86% in population screening in Colorado, USA) develop type 1 diabetes without having a first degree relative with the condition.161 Therefore, with the advent of potential disease-modifying agents (DMAs; see next section), medical–ethical and cost–benefit considerations for public health screening should be considered. A screening programme in Germany detected positive antibodies in 0·3% of 2–5-year-olds in primary care settings.30 Universal screening for coeliac disease and type 1 diabetes identified 0·7% of youth with multiple islet autoantibodies, predicting a 44% 5-year risk of type 1 diabetes.162 In four prospective cohorts enrolling children by age 2·5 years at high risk for type 1 diabetes, 8·5% developed at least one antibody, 5% developed multiple antibodies, and 4% developed the disease. A genetic risk score based on HLA increases the yield for type 1 diabetes classification.163 A 15-year diabetes incidence was reported to be 40% for children with a high-risk HLA profile versus 12% for children with a low-risk profile.164 In a 9–15-year follow-up study of more than 8500 infants with a high risk HLA profile, the 5-year risk for developing multiple antibodies decreased from 4·3% at age 7·5 months to 1·1% by age 6·25 years.165 The authors concluded that screening at age 2 years and at 5–7 years led to the highest sensitivity and positive predictive value.165 Being able to identify people who are at high risk for developing type 1 diabetes not only allows for potential treatment with DMAs, but also informs those at risk to monitor for early symptoms of hyperglycaemia so as to avoid presenting in diabetic ketoacidosis.151

Preventing or halting progression of β-cell demise

A focus of type 1 diabetes research is preventing the autoimmune destruction of the pancreatic β cell.166 Primary strategies to prevent the onset of autoimmunity in infants at high risk for developing type 1 diabetes by modifying diet or introducing supplements in early life have not succeeded.167–169 Antigen-specific immunotherapy has also been attempted in high-risk populations by use of several targets based on observations made in animal models, particularly the non-obese diabetic mouse. Although this model increased our understanding of type 1 diabetes pathophysiology, translation from mouse to human has proved challenging.170 Antigen-specific immunotherapy with oral, subcutaneous, and intranasal insulins have not met their primary endpoints.171–173 Similarly, nicotinamide, which prevented autoimmune diabetes in animal models, did not slow progression from stage 1 to stage 3 diabetes.174 Finally, antigen-specific immunotherapy with glutamic acid decarboxylase prevented diabetes in the non-
obese diabetic mouse but did not halt the disease progression when tested in people who had recently developed stage 3 diabetes.\textsuperscript{175}

**DMAs**

Immunomodulators target both the immune cells and cytokines implicated in \(\beta\)-cell destruction and showed promise in preclinical studies. Abatacept (a soluble CTLA4 fusion protein that blocks co-stimulation and T-cell activation), alefacept (a fusion protein that binds CD4 and CD8 T cells), rituximab (an anti-CD20 monoclonal antibody depleting B cells), and anti-thymocyte globulin (depletes T cells, alters leukocyte–endothelium interactions and dendritic cell functional properties) preserve C-peptide production compared with placebo in newly diagnosed individuals.\textsuperscript{176–179} Of particular interest is the drug teplizumab, an anti-CD3 monoclonal antibody, which delayed progression from stage 2 to stage 3 diabetes by a median of 3 years.\textsuperscript{180,181} Notably, the therapy does require 14 days of intravenous infusion. In November, 2022, teplizumab was approved by the US Food and Drug Administration for the treatment of children older than 8 years with stage 2 diabetes.\textsuperscript{182} Teplizumab is now being tested in early stage 3 diabetes (NCT03875729). Another agent is golimumab, a human IgG1 monoclonal antibody specific for TNF-\(\alpha\); 12-month treatment of individuals in early stage 3 diabetes resulted in a higher C-peptide area under the curve than the placebo.\textsuperscript{183}

The major dilemma for all these interventions is that the effects of immune modulators wane after discontinuation. An intriguing yet untested approach could be modelled after other autoimmune conditions in which intermittent and combined therapy with immunomodulatory compounds could extend the timeline to complete insulin dependency (stage 3; figure 3). There is substantial scope for combination therapy with different immunomodulatory agents. A combination of immunotherapies with either liraglutide\textsuperscript{184} or verapamil\textsuperscript{185} are possibilities. As in other autoimmune diseases, not all participants respond well to the study drug; empirically, it makes sense to administer a therapy and continue it only if the individual exhibits a positive response. However, mechanistic studies are beginning to separate biomarkers that distinguish responders from non-responders, such as follicular helper T-cell populations in abatacept responders.\textsuperscript{186} Accumulating knowledge in this area could help in the delivery of immunomodulators with a precision medicine approach to individuals who will benefit most. There is emerging interest in precision medicine in type 1 diabetes,\textsuperscript{187} and newly identified biomarkers can ultimately be integrated with multiple datasets, such as autoantibody profiles, age of diagnosis, and genetic risk scores, to guide targeted therapeutic interventions. For now, these drugs remain in the category of potential DMAs—a therapeutic option until we can prevent
autoimmunity or develop a biological cure.

The end of the partial remission period is marked by a substantial increase in insulin requirement and a need for close attention to diet and insulin dose calculations. In type 1 diabetes, DMAs can represent an intermediate step to flatten the curve of β-cell demise, prolonging endogenous insulin production until a biological cure is developed (figure 3). For example, patients randomly assigned to golimubab treatment had only a 20% increase in total daily insulin dose during a 12-month period. The ideal DMA will delay the progression from stage 2 to stage 3 diabetes and extend the partial remission period without substantial acute or long-term side-effects (figure 3). A delay of even a few years would alter the timeline for the burden of disease management and the future risk of diabetes complications.

Pharmacoeconomic considerations are an essential factor in the decision to develop current and future DMAs. The diabetes care market was valued at US$69·7 billion in 2019, with an expected compound annual growth rate of 4·5% for the period of 2022–25. Despite the fact that the type 1 diabetes market is growing at a compound annual growth rate of 7·9%, type 1 diabetes represents only 10% of all diabetes cases, with a market share expected to reach only $6·9–9·6 billion in 2025. Stakeholders might therefore evaluate the return on investment given that the mean cost of developing and bringing a drug to market ranges between $314 million and $2·8 billion. This cost is even more pressing when considering that not all participants respond positively to DMAs. This situation creates a difficult economic scenario in which only the pharmaceutical companies willing to take a relatively low profit will invest the capital needed to develop a DMA. If attempts to launch and support population screening do not work, the market would further shrink, making predicted economic gains unreachable.

**Biological treatment**

Exciting progress has been made in the area of β-cell replacement, and several β-cell products have now reached the clinical trial stage. Testing of ViaCyte’s pancreatic progenitor cells is ongoing (NCT03163511) and attempts to reduce their immunogenicity by gene editing are also in progress (NCT05210530). Vertex Pharmaceuticals have also reported early positive signs in the testing of their stem-cell derived β-cell product, with the first participant showing improvements in glycaemia at the 90-day timepoint.

**Future directions**

Great strides have been made in the treatment and management of type 1 diabetes, including faster acting insulin analogues, improved sensors, robust
sensor-augmented pump algorithms, and novel formulations of glucagon. New glycaemic targets that take advantage of extensive data from CGM have been set, recognising that glycaemic variability contributes to negative diabetes outcomes. The exciting advances in β-cell replacement therapy will certainly augment the strides made in technology. The goal of all clinicians should be to optimise glycaemic control for every individual currently living with type 1 diabetes, and to ensure that they receive patient-centred care through a team-based approach. Clearly, more needs to be learned about the role of nutrition and low carbohydrate diets on both diabetes outcomes and overall health, particularly in the paediatric population in which growth and development are essential parameters. An extension of that goal would be to continue researching strategies to prevent the onset and progression of type 1 diabetes. Notable advances have been made, and the coming years will bring more opportunities to focus on specific therapies based on genetic, environmental, and immunological parameters. A world with no more type 1 diabetes seems elusive, yet with each passing year, immunotherapies and other innovative efforts show promise that there will one day be a durable disease prevention or remission strategy for those at risk of developing the disease.


Mastrandrea LD, Wactawski-Wende J, Donahue RP, Hovey KM, Clark A, Quatrin T. Young women with type 1 diabetes have lower bone mineral density that persists over time. *Diabetes Care* 2008; 31: 1729–35.


Melton D. The promise of stem cell medicine. Diabetes Care 2020; 34: 1301–05.


**Figure 1: Average HbA1c by year of age** - Red line represents 2010–12 cohort, and blue line represents 2016–18 cohort. Participants must be contained in both cohorts with at least a 3-year duration for the 2010–12 collection. HbA1c = glycated haemoglobin. *≥80 years old are pooled. Reproduced from Foster et al, by permission of Mary Ann Liebert.
Figure 2: Crosstalk between immune system and target tissue in the pathogenesis of type 1 diabetes
Type 1 diabetes development involves interplay between the immune system (left) and the pancreatic β cells (right). Most cases of type 1 diabetes are likely to involve subtle alterations in immune function; for example, changes mediated by genes in loci associated with T-cell regulation (HLA, CTLA4, PTPN2, PTPN22, and IL2RA), alongside changes in β-cell biology that are either genetic or environmental. Environmental factors can trigger β-cell stress and promote neoantigen generation. Infection can influence β cells by eliciting inflammation and promoting autoimmunity via molecular mimicry, whereby T cells activated in response to a microbial antigen also react with a self-antigen. Monogenic forms of diabetes show the extremes of the dichotomy between the immune system and target tissue: in IPEX syndrome, diabetes maps to regulatory T-cell defects and failed immune regulation, whereas in PERK deficiency, diabetes maps to the β cell. HLA=human leukocyte antigen, IPEX=immune dysregulation, polyendocrinopathy, enteropathy, X-linked. PDL1=programmed death-ligand 1. PERK=protein kinase-like ER kinase.
<table>
<thead>
<tr>
<th>Blood pressure monitoring</th>
<th>Lipid panel*</th>
<th>Urine albumin-to-creatinine ratio (nephropathy)</th>
<th>Dilated fundoscopy (retinopathy)</th>
<th>Glycaemic control</th>
</tr>
</thead>
<tbody>
<tr>
<td>When?</td>
<td>At diagnosis</td>
<td>After diagnosis; age ≥2 years</td>
<td>Puberty or &gt;10 years old (whichever is sooner); or if diabetes duration is &gt;5 years</td>
<td>Puberty or ≥11 years old (whichever is sooner); or if diabetes duration is 3–5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>annually; if abnormal, repeat to confirm 2–3 samples within 6 months</td>
<td>After diagnosis</td>
</tr>
<tr>
<td>Interval</td>
<td>Every clinic visit</td>
<td>If at target, repeat at age 9–11 years; if &lt;100 mg/dL, every 3 years</td>
<td>Urine albumin-to-creatinine ratio &lt;30 mg/g</td>
<td>No retinopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>longer interval if glycaemic control is optimal</td>
<td>Two per year if at goal; With each CGM four times per year if not download at goal</td>
</tr>
<tr>
<td>Target</td>
<td>&lt;90th percentile for age, sex, and height (age &lt;13 years); ≤120/80 mmHg (age ≥13 years)</td>
<td>LDL &lt;100 mg/dL</td>
<td>&lt;7% (≤53 mmol/mol)</td>
<td>&gt;70% (adults)[f]</td>
</tr>
<tr>
<td>Management Lifestyle modification; ACE inhibitor for &gt;95th percentile for age, sex, and height (age &lt;13 years) or ≥130/80 mmHg (age ≥13 years)</td>
<td>Medical nutrition therapy; optimise glycaemic control; start control; ACE inhibitor if statin for children aged &gt;10 years; if LDL &gt;160 mg/dL, or creatinine ratio is elevated if LDL &gt;130 mg/dL and there is a cardiovascular risk</td>
<td>Optimise glycaemic control; refer to ophthalmology</td>
<td>Adjust basal and bolus insulin; additional diabetes education; consider sensor-augmented pump therapy</td>
<td>Adjust basal and bolus insulin; additional diabetes education; consider sensor-augmented pump therapy</td>
</tr>
</tbody>
</table>

Adapted from the 2022 American Diabetes Association Standards of Care."[5, 6]" ACE=angiotensin-converting enzyme. CGM=continuous glucose monitoring. HbA1c=glycated haemoglobin. "TIR (time in range) = 70–180 mg/dL. TIR has not been defined for the paediatric population. "Initial lipid panel can be non-fasting. Allow for improvement in glycaemic control. Random spot sample can be done initially. Targets as high as 8% could be appropriate for individuals with hypoglycaemia unawareness; lower targets are acceptable for individuals with minimal hypoglycaemia. [f] TIR has not been defined for the paediatric population.

**Table:** Current recommendations for screening and treatment of type 1 diabetes comorbidities
Figure 3: Stages of type 1 diabetes diagnosis and the partial remission period

(a) Timeline from stage 1 to stage 3 type 1 diabetes. Diagnosis 1 occurs in stage 2 with dysglycaemia, at a time when the amount of functional β-cell mass is variable. Diagnosis 2 occurs when the need for insulin therapy ensues; the partial remission period is characterised by improved metabolic control with decreased insulin requirement. Diagnosis 3 occurs at the end of the remission period. Patients will require higher insulin doses that increase the risk of hypoglycaemia when attempting to optimise glucose control. This diagnosis is labelled as such because it refers to the traumatic event that is often unexpected by the person with type 1 diabetes (and their family, if applicable). (B) Depiction of the potential effect of a disease-modifying agent in lengthening the timeline from stage 1 to stage 3, and the length of the partial remission period. The dotted line in stage 3B exemplifies the concept that the degree of functional β-cell mass is variable.