Type 1 diabetes

Linda A DiMeglio,
Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA;

Carmella Evans-Molina,
Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA;

Richard A Oram
Institute of Biomedical and Clinical Science, University of Exeter Medical School, and The Academic Kidney Unit, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

Abstract

Type 1 diabetes is a chronic autoimmune disease characterised by insulin deficiency and resultant hyperglycaemia. Knowledge of type 1 diabetes has rapidly increased over the past 25 years, resulting in a broad understanding about many aspects of the disease, including its genetics, epidemiology, immune and β-cell phenotypes, and disease burden. Interventions to preserve β cells have been tested, and several methods to improve clinical disease management have been assessed. However, wide gaps still exist in our understanding of type 1 diabetes and our ability to standardise clinical care and decrease disease-associated complications and burden. This Seminar gives an overview of the current understanding of the disease and potential future directions for research and care.

Introduction

At first consideration, type 1 diabetes pathophysiology and management might seem straightforward; however, the more that is learnt about the disease, the less it seems is truly known. Improved understanding of the disease’s pathogenesis has not led to a single unifying Koch’s postulate for all cases. What once seemed like a single autoimmune disorder, with roots in T-cell mediated attack of insulin-producing β cells, is now recognised to result from a complex interplay between environmental factors and microbiome, genome, metabolism, and immune systems that vary between individual cases.

Despite known genetic underpinnings, most people who are diagnosed with type 1 diabetes do not have a relative with the disease or even the highest risk combination of HLA alleles, making attempts at primary disease prevention difficult. Although survival and patient health have improved considerably, particularly in the past 25 years, a cure for type 1 diabetes remains elusive.1,2 Additionally, despite advances in technology, glycaemic control for most
people with type 1 diabetes is not optimised, and many cannot access modern therapies because of the high costs of even basic care.

In 1984, George Eisenbarth developed a conceptual model for the pathogenesis of type 1 diabetes that is still used nowadays (figure 1). The model plots β-cell mass against age, highlighting an event sequence starting with predisposing genetic risk, then a precipitating environmental trigger that causes islet-specific auto-immunity, followed by β-cell loss, dysglycaemia, clinical diabetes, and rapid progression to complete β-cell loss. Although useful, this model does not address the increasingly apparent complexity of type 1 diabetes pathogenesis. Additionally, the disease pathogenesis is shown by a single line of disease course over time; however, at all stages of the disease heterogeneity exists that is not well understood.

This Seminar provides a review of type 1 diabetes and the status of research in the field. We focus on developments from the past 5 years that highlight the heterogeneity and complexity of the disease.

**Diagnosis**

A diagnosis of diabetes is based on a fasting blood glucose concentration above 7·0 mmol/L (126 mg/dL), a random blood glucose concentration above 11·1 mmol/L (200 mg/dL) with symptoms, or an abnormal result from an oral glucose tolerance test. In the absence of symptoms, abnormal glycaemia must be present on two different occasions. A diagnosis of diabetes can also be made on the basis of a glycated haemoglobin (HbA1c) concentration above 48 mmol/mol (6·5%). However, since dysglycaemia progression can be rapid in patients with type 1 diabetes, HbA1c is less sensitive for diagnosis than fasting or stimulated blood glucose measurements.

Children with type 1 diabetes commonly present with symptoms of polyuria, polydipsia, and weight loss; approximately a third present with diabetic ketoacidosis. The onset of type 1 diabetes can be more variable in adults, who might not present with the classic symptoms seen in children. Although traditional definitions classified type 1 diabetes as juvenile onset, the disease can occur at any age, with up to 50% of cases occurring in adulthood. As many as 50% of adults with type 1 diabetes might be initially misclassified as having type 2 diabetes. Similarly, in conjunction with the epidemic of childhood obesity, type 2 diabetes is increasingly common in adolescents (particularly in non-white individuals), and monogenic diabetes (eg, maturity diabetes onset of the young) accounts for 1–6% of childhood diabetes cases.

Although low C-peptide concentration as a marker of severe endogenous insulin deficiency is useful to guide both classification and treatment in cases of diabetes assessed over 3 years after clinical diagnosis, no single clinical feature can perfectly distinguish type 1 from non-type 1 diabetes at diagnosis. Classification depends on an appreciation of other risk factors for type 1 versus other subtypes and the integration of clinical features (eg, age of diagnosis and body-mass index) with biomarkers (eg, pancreatic autoantibodies).
Over 90% of people with newly diagnosed type 1 diabetes have measurable antibodies against specific β-cell proteins, including insulin, glutamate decarboxylase, islet antigen 2, zinc transporter 8, and tetraspanin-7. Birth cohort studies of individuals with a high genetic risk for diabetes have shown a peak incidence of first autoantibody development before age 2 years. Most people with a single autoantibody do not progress to type 1 diabetes, but seroconversion to the presence of two or more serum autoantibodies in children is associated with an 84% risk of clinical type 1 diabetes by the age of 18 years (figure 2A). The high risk of progression in the presence of multiple autoantibodies has led to a redefining of type 1 diabetes stages. In this new paradigm, a preclinical stage 1 case of type 1 diabetes is defined as the presence of two or more autoantibodies, while stages 2 and 3 are defined as the progression of metabolic abnormalities from abnormal glycaemia to overt diabetes, diagnosed by standard criteria (figure 2B). Since the progression from islet autoantibody positivity to clinical diabetes could take months or years, defining multiple auto-antibody positivity as stage 1 allows targeting of immune interventions to a realistic primary outcome and facilitates early life intervention studies.

Genetics

Type 1 diabetes is a heritable polygenic disease with identical twin concordance of 30–70%, sibling risk of 6–7%, and a risk of 1–9% for children who have a parent with diabetes. The overall lifetime risk varies greatly by country and geographical region but overall is around one in 250 people. The disease is slightly more common in men and boys than in women and girls. Two HLA class 2 haplotypes involved in antigen presentation, HLA DRB1*0301-DQA1*0501-DQB1*0201 (DR3) and HLA DRB1*0401-DQA1*0301-DQB1*0301 (DR4-DQ8), are linked to approximately 50% of disease heritability and are prevalent in white people. Other haplotypes are known to reduce type 1 diabetes risk, including DRB1*1501-DQA1*0102-DQB1*0602 (DR15-DQ6). The mechanisms by which these HLA haplotypes interact and alter risk are not completely understood. Different HLA associations in other racial groups are recognised but remain poorly characterised. Genome-wide association studies have identified over 60 additional non-HLA loci associated with the risk of type 1 diabetes. These variants have been predominantly associated with the immune system and highlight pathways that are important in disease development—e.g., insulin gene expression in the thymus, regulation of T-cell activation, and viral responses. These HLA and non-HLA genetic associations could identify potential targets for future disease-modifying therapies or subgroups of patients who could benefit from specific immune interventions.

Historically, people at high risk of type 1 diabetes have been identified for research by HLA risk or familial risk, or both. By contrast, individual non-HLA loci cannot be used to predict type 1 diabetes or discriminate it from other types of diabetes. Combined measurement of HLA and non-HLA loci into genetic risk scores could offer improved prediction of the risk of developing type 1 diabetes and discrimination of type 1 from type 2 diabetes. Furthermore, the continuing fall of genotyping costs could facilitate future population-level disease prediction by use of genetic risk scores.
Epidemiology

Globally, type 1 diabetes is increasing both in incidence and prevalence, with overall annual increases in incidence of about 2–3% per year. US data suggest an overall annualised incidence from 2001 to 2015 of about 22·9 cases per 100 000 people among those younger than 65 years; data from other regions suggest similar incidences. The greatest observed increases in incidence of type 1 diabetes are among children younger than 15 years, particularly in those younger than 5 years. These increases cannot be explained by genetic changes, implicating environmental or behavioural factors, or both. Many environmental exposures are associated with type 1 diabetes, including infant and adult diet, vitamin D sufficiency, early-life exposure to viruses associated with islet inflammation (eg, enteroviruses), and decreased gut-microbiome diversity. Obesity is associated with increasing presentation of type 1 diabetes, with β-cell stress potentially providing a mechanistic underpinning. The large differences in the incidence of type 1 diabetes in genetically similar populations that are separated by socioeconomic borders and the increasing incidence of type 1 diabetes in genetically low-risk individuals highlight the importance of environmental risk factors regardless of genetic background risk. Further work is being done to understand the role of gene–environment interactions in the pathogenesis of type 1 diabetes, the role of different loci and pathways at different stages of the disease, and whether loci that are independent of disease risk could have a role in disease progression after development of autoimmunity. Some data suggest that the observed incidence could be declining in adults or potentially even levelling off across all age ranges; worldwide registry data will eventually reveal if this pattern is indeed true.

The incidence of type 1 diabetes varies by country and by region within countries. At northern latitudes, people born in the spring are more likely to develop the disease than those born in the other seasons. The peak incidence of diagnosis is seen in children aged 10–14 years. Although many people present with type 1 diabetes in adulthood, the higher incidence of type 2 diabetes in adulthood compared with type 1 diabetes and the flawed criteria for distinguishing these forms of disease make assessment of the incidence of type 1 diabetes in adults very difficult. Most people living with type 1 diabetes are adults.

The immune phenotype of type 1 diabetes

The pathogenesis of type 1 diabetes results from a complex interaction between the pancreatic β-cell and innate and adaptive immune systems (figure 3). The question of whether a trigger for the immune response against β cells exists or whether the immune response is a random stochastic event has been a subject of considerable speculation and controversy. Several viral infections are associated with type 1 diabetes, with enterovirus being one of the most commonly associated infections. Enteroviral major capsid protein VP1 and RNA have been detected in islets from people with recent-onset type 1 diabetes, along with hyper-expression of the class 1 major histo compatibility complex and other indices of viral infection. One possibility is that some people with type 1 diabetes have an atypical, chronic viral infection of β cells, leading to chronic inflammation and the development of autoimmunity. The viral hypothesis has been difficult to test, although both
antiviral therapy and the development of vaccines targeting enteroviruses are being pursued for this purpose.

In the field, much effort has been given to the study of the adaptive immune system in type 1 diabetes by use of assays of peripheral lymphocytes selected for autoreactivity to islet antigens. Increased frequency of islet-specific autoreactive CD8+ T lymphocytes and decreased regulatory immune function have been associated with type 1 diabetes. Experiments, such as the transfer of type 1 diabetes following non-T-cell depleted allogeneic bone-marrow transplantation, development of type 1 diabetes in an individual with B-lymphocyte and antibody deficiency, and inherited genetic defects of T-lymphocyte function causing type 1 diabetes highlight the crucial role of T cells in the pathophysiology of type 1 diabetes. Almost all studies of peripheral autoimmunity in people with type 1 diabetes show overlap of phenotypes seen in the general population, and the proportion of islet autoreactive cells present in the periphery is often tiny (only a few cells among millions of non-autoreactive cells). As a result, connecting the population of autoreactive immune cells that is detectable in blood to the disease process in islets has been difficult. A key development has been the isolation of T lymphocytes that are reactive to β-cell antigen peptides from islets of organ donors with type 1 diabetes.

Histopathologically, these processes are observed as insulitis or immune-infiltrated (insulitic) islets. CD8+ T lymphocytes are the most common immune cells within insulitic lesions, with CD4+ T cells present in lower numbers. Distinct patterns of insulitis that stratify with the aggressiveness of β-cell loss and age of diagnosis have been identified in insulitic islets. Although insulitis is common and intense in animal models of type 1 diabetes, it is much rarer and more variable in human beings (figure 3).

The β-cell phenotype of type 1 diabetes

At diagnosis, people with type 1 diabetes have reduced β-cell function compared with healthy controls. With amelioration of hyperglycaemia, these β cells can have a partial recovery of insulin secretory function, leading to a so-called honeymoon period after diagnosis with minimal or no exogenous insulin needed. Over time, many of these residual cells are lost. However, analysis of pancreatic sections from individuals with long-term type 1 diabetes show the presence of residual β cells decades after diagnosis. When sensitive C-peptide measurements are performed, 30–80% of people with long-term type 1 diabetes are found to be insulin microsecretors. So, although endogenous β-cell quantity and function decline with longer disease duration, this decline does not progress to a complete loss of all β cells. This finding is noteworthy because in the Diabetes Control and Complications Trial persistent C-peptide secretion was associated with reduced development of retinopathy, nephropathy, and hypoglycaemia. Additionally, the persistence of C-peptide secretion in people with long-term type 1 diabetes could improve glucagon responses to hypoglycaemia. Moreover, the presence of residual C-peptide secretion after the diagnosis of disease could also increase the possibility of an improved effect of interventions targeted at rescuing or augmenting the survival of this residual pool of β cells. Analyses of pancreatic specimens from the Network of Pancreatic Organ Donors repository have not found evidence of either increased neogenesis or proliferation in pancreatic cells.
from donors with type 1 diabetes. Thus, the mechanisms underlying the persistence of residual β cells in people with long-term type 1 diabetes remain unclear. Identifying pathways that have allowed these cells to escape the autoimmune attack could yield insight into new therapeutic approaches.

β-cell abnormalities might also contribute to type 1 diabetes pathogenesis, leading to the notion of so-called β-cell suicide. β-cell HLA class I overexpression is common in pancreatic sections from cadaveric donors with type 1 diabetes. This overexpression serves as a homing signal for cytotoxic T lymphocytes. However, whether this signal is a primary β-cell defect or a response to a stimulus (eg, a viral infection) is not yet known. Additionally, evidence also exists for increased β-cell endoplasmic reticulum stress linked with accelerated β-cell death. Endoplasmic reticulum stress in β cells has also been associated with alterations in mRNA splicing and errors in protein translation and folding; the resultant protein products have been proposed as potential immunogenic neoantigens.

In addition to these defects in the β-cell compartment, alterations in non-endocrine islet cells and the exocrine pancreas have also been described (figure 4). These defects include abnormalities in the islet extracellular matrix and in islet innervation and vascularity. Data have also placed a renewed emphasis on the role of exocrine pancreatic pathology in type 1 diabetes. Compared with healthy individuals, people with type 1 diabetes have a decreased pancreatic weight and volume that continues to decrease with disease duration. This finding could be explained by developmental defects, or pancreatic atrophy in response to loss of the paracrine and pro-growth effects of insulin or chronic inflammation, or even autoimmune-mediated exocrine destruction. These possibilities are all topics of active investigation.

Management of clinical disease

Methods of managing type 1 diabetes continue to improve, and although progress is generally slow and incremental, occasionally it is punctuated by rapid change. One such moment of change happened in 1993 with the publication of the Diabetes Control and Complication Trial. This trial and the follow-up observational Epidemiology of Diabetes Interventions and Complications trial convincingly showed that achieving and maintaining glucose concentrations as close to those seen in people without diabetes as possible leads to a reduction in microvascular and cardiovascular type 1 diabetes complications.

Although insulin remains the mainstay of therapy, new insulin analogues with varying onsets and durations of action are widely available. Optimal glycaemic control requires multiple-dose insulin regimens that mimic physiological insulin release, with basal insulin for overnight and between-meal control, plus bolus doses of rapid-acting insulin analogues to cover ingested carbohydrate loads and treat hyperglycaemia. Insulin can be taken by injection (with an insulin pen if available) or, preferably for many people, with an insulin pump. Ultra-rapid inhaled insulin is also available, but little enthusiasm for this preparation exists because of its fixed dosing (four or eight unit increments only), issues with consistent delivery, cost, and the need for pulmonary function testing. A faster-acting subcutaneously-administered insulin (via injection or infusion) has also recently become available.
available for clinical use. Appropriate insulin use requires frequent dosing adjustments for ingested carbohydrates, physical activity, and illness or stress.

While pramlintide is the only non-insulin medication approved for improved glycaemic control in patients with type 1 diabetes, metformin, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose co-transporter-2 (SGLT2) inhibitors have also been used off-label; however, fewer than 5% of patients use these medications. Metformin, an insulin sensitiser, is the most commonly prescribed drug for people with type 1 diabetes who have insulin resistance but it has not been shown to be effective in people younger than 18 years who are overweight or obese and have type 1 diabetes. Use of SGLT2 inhibitors is restricted in part because of early reports of euglycaemic diabetic ketoacidosis in people with type 1 diabetes treated with these compounds. A 2018 meta-analysis of these inhibitors suggests they are safe, but more data are needed.

Glucagon therapy is also poised to undergo a resurgence in management of type 1 diabetes. Although only an emergency kit has been commercially available up until now for cases of severe hypoglycaemia leading to seizure or loss of consciousness, nasal and stable liquid formulations are being developed. The nasal formulation will be available as a rapid rescue therapy only, whereas the stable liquid formulation could also be used in small doses for exercise and in dual hormone (ie, insulin and glucagon) closed-loop systems.

In the past 13 years, continuous glucose monitoring (CGM) and intermittently viewed CGM devices for at-home patient use with minimally invasive devices have become available, which have similar accuracy to capillary blood glucose monitors. Both CGM and intermittently viewed CGM allow examination of glucose concentration patterns over time and, although CGM devices still need periodic calibration, they obviate the need for frequent capillary blood glucose measurements. CGM is more sophisticated than intermittently viewed CGM because it can give the user a warning on the basis of absolute or projected glucose values. When CGM is incorporated into hybrid closed-loop insulin-pump systems that automatically regulate basal infusion rates, but that require manual delivery of meal boluses by trained wearers to cover estimated carbohydrate intakes, substantial improvements in glucose variability and overall glycaemic control are seen (figure 5). Combined use of automated insulin delivery and CGM offers the prospect of an artificial pancreas with little input from the user. The substantial advances that have been made in pump and sensor technology and the increase in the number of trials to test their efficacy show that partially or fully automated systems could become a reality.

Guidelines from the American Diabetes Association, International Society for Pediatric and Adolescent Diabetes, and Canadian Diabetes Association suggest a HbA1c target of less than 53 mmol/mol (7.0%) for adults and less than 58 mmol/mol (7.5%) in paediatric patients with type 1 diabetes, however, most individuals do not achieve these targets. Although setting more aggressive targets is associated with achieving lower HbA1c, these targets should be individualised on the basis of many factors including comorbidities, patient capability and attitude, and available care resources—eg, even lower targets are often prescribed for pregnant women and women anticipating pregnancy than those prescribed to
other patients. Higher targets might be appropriate for people with hypoglycaemia unawareness, history of severe hypoglycaemia, advanced complications, and short life expectancy. For optimal outcomes, people with diabetes should be cared for by a multidisciplinary care team, including diabetes educators, nurse practitioners, nurses, nutritionists, physician assistants, exercise physiologists, social workers, and psychologists. To optimise glycaemic control, clinical care with skilled and structured patient education and training sessions should be provided—including information on insulin adjustments, carbohydrate counting, and optimal use of available technology.

People with type 1 diabetes also risk developing other autoimmune diseases, sometimes as part of a poly-glandular autoimmune syndrome. A study from the Type 1 Diabetes Exchange clinic registry noted the prevalence of autoimmune disease was 27% in a population of over 25,000 people with type 1 diabetes with a mean age of 23 years. The most common autoimmune disease is autoimmune thyroiditis (ie, Hashimoto thyroiditis and Graves’ disease) followed by coeliac disease. Other associated conditions include collagen-vascular diseases (eg, rheumatoid arthritis and lupus), autoimmune gastritis or pernicious anaemia, vitiligo, and Addison’s disease. Guidelines for the care of people with diabetes include periodic screening for these diseases, particularly thyroid and coeliac diseases.

Complications of type 1 diabetes

The discovery of insulin in 1922 transformed type 1 diabetes from a terminal to a treatable disease. Despite the advances in care discussed previously, the disease continues to be associated with substantial medical, psychological, and financial burden. Hypoglycaemia and ketoacidosis are persistent potentially life-threatening complications. Severe hypoglycaemic events requiring treatment assistance from another person occur at rates of 16–20 per 100 person-years; hypoglycaemic events leading to loss of consciousness or seizure occur at a rate of 2–8 per 100 person-years. Recurrent hypoglycaemia results in an increased likelihood of hypoglycaemia unawareness and subsequent severe hypoglycaemic events, since recurrent hypoglycaemia reduces the glucose concentration that triggers the counter-regulatory responses to return to euglycaemia. Hypoglycaemia unawareness can improve with education, support, and glucose targets that are aimed at avoiding biochemical hypoglycaemia, while maintaining overall metabolic control.

Hypoglycaemic events are associated with adverse effects on cognitive function and are associated with 4–10% of type 1 diabetes-related deaths. Observational studies suggest poor diabetes control does not reduce the risk of severe hypoglycaemia. Notably, rates of severe hypoglycaemic events have been decreasing over time and with CGM and other advanced diabetes technologies HbA1c can be lowered into the target range without increasing the risk of severe hypoglycaemia. Treatment in hospital for diabetic ketoacidosis occurs at a rate of 1–10 per 100 patient-years in paediatric populations with established type 1 diabetes, and accounts for 13–19% of type 1 diabetes-related mortality. Incidence of diabetic ketoacidosis is higher among women than among men, and among people with higher HbA1c levels than other people with type 1 diabetes.
Microvascular complications of the disease manifest primarily as retinopathy, neuropathy, and nephropathy, but also can affect cognitive function, the heart, and other organs. Hyperglycaemia is the primary risk factor for microvascular disease, and reducing HbA1c through intensive diabetes management, particularly early during disease, is associated with striking (about 70%) reductions in incidence and slower progression of microvascular disease. However, differences in HbA1c do not fully explain the variation in the incidence of complications and the severity of disease between individuals. Variability in glucose concentrations (both during the day and longer term) and glycosylation rates also probably have a role in interindividual differences. Type 1 diabetes during puberty also appears to accelerate the development of complications.

Macrovascular complications of type 1 diabetes include atherosclerosis and thrombosis in the heart, peripheral arteries, and brain. By contrast with microvascular complications, the risk of cardiovascular complications does not appear to be as attenuated by intensive blood sugar control. Diabetic nephropathy, whether manifesting as microalbuminuria, macroalbuminuria, or a reduced glomerular filtration rate progressively augments the overall risk of macrovascular complications. Cardiovascular disease remains the major cause of premature morbidity and mortality, with data suggesting an 8–13-year shorter life expectancy for people with type 1 diabetes than for healthy individuals.

People with diabetes might also have both chronic and acute neurocognitive changes that include decline in cognitive function with detrimental effects on psychomotor speed, cognitive flexibility, attention, and visual perception. Although the pathophysiology of neurocognitive changes is poorly understood, their development has been linked with both microvascular and macrovascular changes and changes in brain structure, neuronal loss, and cerebral atrophy. Risk factors include developing diabetes early in life, chronic hyperglycaemia, and repeated hypoglycaemia.

In the past 25 years, among people with type 1 diabetes the risks of microvascular and macrovascular complications have substantially decreased and outcomes have improved. These improvements have been largely driven by better glycaemic control and improved management of associated risk factors—eg, hypertension and hyperlipidaemia. Several studies have identified additional non-glycaemic risk factors for the development of complications. Genetic studies have not yielded strong associations between specific gene variants and complication status. Low levels of education and income have been associated with high risks of both microvascular and macrovascular complications. Sex also appears to modify risk, since women with type 1 diabetes have been shown to have higher rates of all-cause premature mortality and vascular events than do men with type 1 diabetes. In the past 5 years, new technologies have been designed to attempt to better predict future risk and complications by combining risk factors into probability models. Two examples are the QDiabetes and QRISK3 web calculators that were developed with a prospective general practice dataset of 803,044 people with diabetes (44,440 with type 1 diabetes). These calculators can be used to predict 10-year risk for microvascular and macrovascular complications. However, continued work is needed in this area to combine prediction models with disease-specific biomarkers and disease-modifying therapies that can prevent sequelae.

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An additional noteworthy complication of type 1 diabetes is the patient-reported burden of adverse also their family, friends, and caregivers.\textsuperscript{131} Fear of hypoglycaemia is a prevalent issue, particularly for the families of very young children with type 1 diabetes.\textsuperscript{132} Furthermore, poor quality of life is predictive of subsequent poor glycaemic control.\textsuperscript{133}

### Disease-modifying therapies

For over 30 years, most efforts to cure type 1 diabetes have focused on altering the immune system’s attack on \( \beta \) cells. This approach began with trials of ciclosporin, an immunosuppressant that was given to inhibit T-cell activation. Although ciclosporin was unable to induce a durable disease remission, insulin requirements of patients decreased during active treatment, generating enthusiasm that immune modulation could treat type 1 diabetes.\textsuperscript{134–136} Subsequently, other strategies have been tested in both primary and secondary prevention paradigms. Most efforts have focused broadly on tolerance induction by use of antigens or modulation of T-lymphocyte, B-lymphocyte, and cytokine responses. Some primary prevention studies have also used dietary approaches.\textsuperscript{137,138}

Antigen-based trials have used various forms of glutamate decarboxylase (GAD) protein, which have shown mixed but mostly negative results.\textsuperscript{139–141} The Diabetes Prevention Trial Type 1, tested whether oral or parental insulin prevented the development of type 1 diabetes in people who were autoantibody positive. Neither approach reduced diabetes development, but subgroup analyses suggested a benefit of oral insulin in individuals with the highest titres of insulin auto-antibodies.\textsuperscript{142,143} Based on this finding, the Type 1 Diabetes TrialNet Network completed a trial\textsuperscript{144} of low-dose oral insulin in a second cohort of individuals who were autoantibody positive with similar insulin autoantibody profiles, but this trial was also negative. Negative results were also observed in another trial investigating intranasal insulin.\textsuperscript{145}

Personalised strategies for tolerance induction are now also being pursued. One study tested repeated intradermal doses of a specific proinsulin peptide fragment in people with the \textit{HLA} \textit{DRA}1*0401 genotype,\textsuperscript{146} for whom this peptide was identified to be specifically immunogenic. Clinical trials at diagnosis have also tested approaches aimed at modulating T-cell and B-cell responses. Despite many attempts at immune intervention, only four categories of drugs have shown efficacy in preserving C-peptide secretion in recent onset type 1 diabetes in randomised placebocontrolled trials. These drugs include a monoclonal antibody against the B-cell CD20 receptor (rituximab),\textsuperscript{147} monoclonal antibodies against the T-cell CD3 receptor (teplizumab\textsuperscript{148,149} and otelixizumab\textsuperscript{150}), cytotoxic T-lymphocyte protein 4 (CTLA4)-immunoglobulin-mediated co-stimulatory blockade with abatacept,\textsuperscript{151} and alefacept,\textsuperscript{152} which is a fusion protein that binds CD2 and targets CD4+ and CD8+ effector memory T cells. Although the phase 2 trials of these drugs met their primary or secondary endpoints, defined as an improvement in the C-peptide area-under-the-curve response during a mixed meal tolerance test, no drug has yet been able to induce insulin independence or progressed to a positive phase 3 trial that was translatable into clinical care. This gap in translating results from trials into clinical practice could highlight the need for alternative strategies. Combinatorial approaches that modulate multiple aspects of the immune response could result in better efficacy. For example, low-dose anti-thymocyte
globulin in combination with granulocyte colony-stimulating factor has shown early and sustained efficacy in pilot studies\textsuperscript{153,154} and is being tested in a phase 2 study\textsuperscript{(1)} in recent-onset type 1 diabetes. Another approach is to intervene earlier in the disease process, at a time when greater β-cell mass remains. To this end, abatacept\textsuperscript{(1)} and teplizumab\textsuperscript{(1)} are being tested in stage 1 and stage 2 type 1 diabetes through the TrialNet Network. Even modest preservation of β-cell function could have long-term benefits, and better glycaemic control early in the disease course could mitigate the likelihood of complications.\textsuperscript{155–157}

One potential future therapy for type 1 diabetes is with replacement of β cells from an external source. Pancreas transplants have been performed for over 50 years and have become a standard-of-care treatment in individuals who have developed end-stage renal failure and require kidney transplantation.\textsuperscript{158} Simultaneous kidney and pancreas transplantation in experienced centres can offer an up to 80% chance of insulin independence for over 5 years, but there is substantial surgical risk, and the requirement of immunosuppression.\textsuperscript{159} Islet transplantation is a low-risk procedure, with donor islets infused into the liver via the portal vein. Shapiro and colleagues’ landmark work, by use of a steroid free Edmonton Protocol,\textsuperscript{160} showed that islet transplantation could achieve insulin independence and offered an example of a successful and low-risk cell-based therapy. However, only a minority of islet transplant recipients achieve durable insulin independence. Moreover, morbidity associated with immunosuppression and limitations in the supply of donor islets restricts the number of people who can benefit from islet transplantation.\textsuperscript{161} Currently, islet transplantation is used in a small subset of patients who have extremely severe hypoglycaemic unawareness. Even if insulin independence is not achieved, severe life-threatening hypoglycaemia can be prevented with minimal islet transplant function.\textsuperscript{162,163}

Cell therapy as a potential cure for type 1 diabetes remains a field of great interest.\textsuperscript{2} Considerable effort has been focused on protocols to generate functional and glucose-responsive β cells from human embryonic stem cells or induced pluripotent stem cells from living donors. This approach offers the possibility of a limitless source of β cells that could be delivered in a semipermeable device that would permit functional insulin secretion but avoid the need for immunosuppression.\textsuperscript{164} Several small molecules, growth factors, hormones, and nutrients have been shown to promote modest β-cell neogenesis and proliferation. However, most positive results come from animal models and have been difficult to replicate in human studies. While stem-cell-based therapies and neogenesis are a source of hope for potential cures, they are not realistic treatments in the immediate future.\textsuperscript{2}

Other novel approaches include autologous haemopoietic stem-cell transplantation\textsuperscript{165,166} and autologous T-regulatory cell administration.\textsuperscript{167–169} In response to growing evidence highlighting an active role for the β cell in disease pathogenesis, several ongoing trials are testing drugs that have successfully targeted β-cell stress responses in mouse models of diabetes.\textsuperscript{170}
Conclusions

Over the past 50 years, people with type 1 diabetes and their medical-care providers have been tantalised with optimism and subsequently disappointed at the seemingly unobtainable cure on the horizon. However, this long journey has been punctuated by several pivotal successes, including the discovery of insulin in 1922, the first pancreatic transplantation in 1966, the first insulin-pump studies, the first immunomodulatory trial in 1986, and the first definitive evidence linking glycaemic control with complication status in 1993. The past 25 years has brought an upsurge of technological advances, including designer insulin analogues, smart insulin pumps, continuous glucose sensors, and closed-loop insulin delivery systems.

Clinicians, investigators, and patients have gained a better appreciation of the true complexity of type 1 diabetes, and humility in the face of many unsuccessful trials aimed at inducing a durable disease remission. While scientists continue to untangle the complicated pathogenesis of the disease, patients and health-care providers should focus on advocating for improved access to modern advances in diabetes care, especially for affordable insulin analogues and technologies that can reduce the burden of managing this chronic disease. When insulin was discovered, the University of Toronto freely licensed the right to manufacture the drug; yet, people in resource-limited environments continue to die because they have no access to insulin.

Additionally, crucial research must continue into strategies to prevent disease onset and preserve or restore β-cell function. These approaches offer the promise of ameliorating or eliminating disease complications, and greatly improving outcomes for those who have the disease. Continued development of new low-cost, low-burden, and highly effective therapies to improve glycaemic control is also needed. These approaches could include investigation into the effects of different dietary composition on glycaemic outcomes, and the safety and efficacy of open-source patient-designed artificial pancreas innovations. Given observed differences in care, health-care providers must be committed to initiatives for continuous quality improvement, with a focus on increasing uptake and implementation of best standards of care. A greater focus on patient-centred outcomes has been present in trials, and further exploration of these important endpoints is also crucial. If stakeholders in the field concentrate on the areas that are most likely to have a long-term effect, management of type 1 diabetes is poised to undergo further radical transformation.

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Search strategy and selection criteria

We searched MEDLINE for publications in English published between Jan 1, 2014, and March 1, 2018, using the term “type 1 diabetes” and MEDLINE subheadings and selected papers on the basis of our opinion of their scientific importance. Research published since the 2014 *Lancet* Seminar on this topic was given particular attention. We provide an overview of type 1 diabetes focusing on updating the reader on recent advances and controversies.
Figure 1: Challenges to the Eisenbarth model of the natural history of type 1 diabetes

Key events of the Eisenbarth model over the course of the disease (measured in years) are shown by dotted lines at different time points. Challenges to this model, taking into account the increasing complexity of type 1 diabetes, include the following: precipitating immune events that might occur prenatally (A); large variation in starting β-cell mass and function, defects in one or both could be developmentally programmed (B); initiation of autoimmunity is measured by autoantibodies, but other immunological abnormalities probably precede the presence of detectable pancreatic antibodies (C); the patient’s environment could affect their entire disease course (D); β-cell loss could relapse or remit (E); dysglycaemia occurs before clinical diagnosis (F); decline in β-cell function might not mirror decline in β-cell mass—methods to measure β-cell mass have not been established (G); and residual C-peptide is detectable in many people who have long duration type 1 diabetes (H). Furthermore, progression through stages A–C is heterogeneous, and will be affected by immune, genetic, environment, and key demographic features (ie, age, body-mass index). Adapted from Atkinson et al. 4
Figure 2: Factors contributing and disease progression to type 1 diabetes

(A) The probability of developing diabetes in childhood stratified by the number of islet antibodies. In a study by Zeigler and colleagues, 16 13 377 children were identified as at risk in the newborn or infant period on the basis of high-risk HLA genotypes or having a relative with type 1 diabetes, or both, and were followed-up regularly. The numbers at risk are the number of children receiving follow-up at ages 0, 5, 10, 15, and 20 years. Adapted from Ziegler et al 16 with permission of the American Medical Association. (B) Type 1 diabetes progression and stages of type 1 diabetes. Stage 1 is the start of type 1 diabetes, marked by individuals having two or more diabetes-related autoantibodies and normal blood sugar concentrations. In stage 2, individuals have dysglycaemia without symptoms. Stage 3 is the time of clinical diagnosis. Reproduced from Greenbaum et al 17 with permission from the American Diabetes Association. T1D=type 1 diabetes.
The development of type 1 diabetes is thought to be initiated by the presentation of \(\beta\)-cell peptides by antigen-presenting cell (APCs). APCs bearing these autoantigens migrate to the pancreatic lymph nodes where they interact with autoreactive CD4+ T lymphocytes, which in turn mediate the activation of autoreactive CD8+ T cells (A). These activated CD8+ T cells return to the islet and lyse \(\beta\) cells expressing immunogenic self-antigens on major histocompatibility complex class I surface molecules (B). \(\beta\)-cell destruction is further exacerbated by the release of proinflammatory cytokines and reactive oxygen species from innate immune cells (macrophages, natural killer cells, and neutrophils; C). This entire process is amplified by defects in regulatory T lymphocytes, which do not effectively suppress autoimmunity (D). Activated T cells within the pancreatic lymph node also stimulate B lymphocytes to produce autoantibodies against \(\beta\)-cell proteins. These autoantibodies can be measured in circulation and are considered a defining biomarker of type 1 diabetes (E).

**Figure 3: The immunopathogenesis of type 1 diabetes**

The development of type 1 diabetes is thought to be initiated by the presentation of \(\beta\)-cell peptides by antigen-presenting cell (APCs). APCs bearing these autoantigens migrate to the pancreatic lymph nodes where they interact with autoreactive CD4+ T lymphocytes, which in turn mediate the activation of autoreactive CD8+ T cells (A). These activated CD8+ T cells return to the islet and lyse \(\beta\) cells expressing immunogenic self-antigens on major histocompatibility complex class I surface molecules (B). \(\beta\)-cell destruction is further exacerbated by the release of proinflammatory cytokines and reactive oxygen species from innate immune cells (macrophages, natural killer cells, and neutrophils; C). This entire process is amplified by defects in regulatory T lymphocytes, which do not effectively suppress autoimmunity (D). Activated T cells within the pancreatic lymph node also stimulate B lymphocytes to produce autoantibodies against \(\beta\)-cell proteins. These autoantibodies can be measured in circulation and are considered a defining biomarker of type 1 diabetes (E).
Figure 4: Pancreatic and islet abnormalities in type 1 diabetes

(A) Type 1 diabetes is characterised by a variety of abnormalities that involve both the islet and the exocrine pancreas. The hallmark of type 1 diabetes is loss of insulin-producing $\beta$ cells and immune infiltration of islets. However, the presence of insulitis, even within an individual pancreas, can be highly variable. (B) Immunofluorescent image of an insulitic islet from a cadaveric donor with long-term type 1 diabetes. Insulin is shown in blue and CD8+ T cells surrounding the islet are shown in yellow. (C) Haematoxylin and eosin staining of an islet from a cadaveric donor that exhibits a classic pattern of insulitis. The islet is circled with a yellow dotted line. The infiltrating immune cells are circled in red and indicated by arrows. (D) Haematoxylin and eosin staining of an islet, circled in yellow dotted line, from a cadaveric donor with long-term type 1 diabetes without any discernible immune infiltrate. By contrast with the islet in (C), this islet has evidence of peri-islet fibrosis as shown circled in red and indicated by arrows. Images B–D courtesy of M Campbell-Thompson, University of Florida, Gainesville, FL, USA.
Figure 5: Glucose concentrations in patients with type 1 diabetes with a hybrid closed-loop system, before and after use, over 24 h

Sensor glucose profiles from 124 people with type 1 diabetes, of which 30 were adolescents (14–21 years; A) and 94 were adults (22–75 years; B), before (during run-in phase) and during the study phase using the Medtronic MiniMed 670 g hybrid closed-loop system (Medtronic, Northridge CA, USA) under clinical trial conditions. Median and IQR of sensor glucose values are given as a green line and band for the run-in phase, and a pink line and band for the study phase, respectively. In the run-in phase, the hybrid closed-loop system was in manual mode, with participants making all treatment decisions except for the pump automatically suspending before sensor glucose concentrations became too low. In the study phase, the hybrid closed-loop system was in auto mode. Participants had less variability in their blood glucose concentration during auto mode. Reproduced from Garg et al,92 with permission from Mary Ann Liebert.