

New advances in type 1 diabetes

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Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

ABSTRACT

Type 1 diabetes is an autoimmune condition resulting in insulin deficiency and eventual loss of pancreatic β cell function requiring lifelong insulin therapy. Since the discovery of insulin more than 100 years ago, vast advances in treatments have improved care for many people with type 1 diabetes. Ongoing research on the genetics and immunology of type 1 diabetes and on interventions to modify disease course and preserve β cell function have expanded our broad understanding of this condition. Biomarkers of type 1 diabetes are detectable months to years before development of overt disease, and three stages of diabetes are now recognized. The advent of continuous glucose monitoring and the newer automated insulin delivery systems have changed the landscape of type 1 diabetes management and are associated with improved glycated hemoglobin and decreased hypoglycemia. Adjunctive therapies such as sodium glucose cotransporter-1 inhibitors and glucagon-like peptide 1 receptor agonists may find use in management in the future. Despite these rapid advances in the field, people living in under-resourced parts of the world struggle to obtain necessities such as insulin, syringes, and blood glucose monitoring essential for managing this condition. This review covers recent developments in diagnosis and treatment and future directions in the broad field of type 1 diabetes.

Introduction

Type 1 diabetes is an autoimmune condition that occurs as a result of destruction of the insulin producing β cells of the pancreatic islets, usually leading to severe endogenous insulin deficiency.¹ Without treatment, diabetic ketoacidosis will develop and eventually death will follow; thus, lifelong insulin therapy is needed for survival. Type 1 diabetes represents 5-10% of all diabetes, and diagnosis classically occurs in children but can also occur in adulthood. The burden of type 1 diabetes is expansive; it can result in long term complications, decreased life expectancy, and reduced quality of life and can add significant financial burden. Despite vast improvements in insulin, insulin delivery, and glucose monitoring technology, a large proportion of people with type 1 diabetes do not achieve glycemic goals. The massive burden of type 1 diabetes for patients and their families needs to be appreciated. The calculation and timing of prandial insulin dosing, often from food with unknown carbohydrate content, appropriate food and insulin dosing when exercising, and cost of therapy are all major challenges. The psychological realities of both acute management and the prospect of chronic complications add to the burden. Education programs and consistent surveillance for “diabetes burnout” are ideally available to everyone with type 1 diabetes.

In this review, we discuss recent developments in the rapidly changing landscape of type 1 diabetes

and highlight aspects of current epidemiology and advances in diagnosis, technology, and management. We do not cover the breadth of complications of diabetes or certain unique scenarios including psychosocial aspects of type 1 diabetes management, management aspects specific to older adults, and β cell replacement therapies. Our review is intended for the clinical reader, including general internists, family practitioners, and endocrinologists, but we acknowledge the critical role that people living with type 1 diabetes and their families play in the ongoing efforts to understand this lifelong condition.

Sources and selection criteria

We did individual searches for studies on PubMed by using terms relevant to the specific topics covered in this review pertaining to type 1 diabetes. Search terms used included “type 1 diabetes” and each individual topic—diagnosis, autoantibodies, adjuvant therapies, continuous glucose monitoring, automated insulin delivery, immunotherapies, diabetic ketoacidosis, hypoglycemia, and under-resourced settings. We considered all studies published in the English language between 1 January 2001 and 31 January 2023. We selected publications outside of this timeline on the basis of relevance to each topic. We also supplemented our search strategy by a hand search of the references of key articles. We prioritized studies on each highlighted topic according to the level of evidence (randomized controlled trials (RCTs),

Table 1 | Autoantibody characteristics associated with increased risk of type 1 diabetes¹⁰

Characteristic	Insulin autoantibody	Glutamic acid decarboxylase autoantibody	Islet antigen 2 autoantibody	Zinc transporter 8 autoantibody
Age of appearance	High risk in young children	Associated with risk in older cohorts	High risk for all ages	Associated with risk in older cohorts
Titer	High titer in all ages	High titer early after seroconversion	High titer, time constant	No association found to date

systematic reviews and meta-analyses, consensus statements, and high quality observational studies), study size (we prioritized studies with at least 50 participants when available), and time of publication (we prioritized studies published since 2003 except for the landmark Diabetes Control and Complications Trial and a historical paper by Tuomi on diabetes autoantibodies, both from 1993). For topics on which evidence from RCTs was unavailable, we included other study types of the highest level of evidence available. To cover all important clinical aspects of the broad array of topics covered in this review, we included additional publications such as clinical reviews as appropriate on the basis of clinical relevance to both patients and clinicians in our opinion.

Epidemiology

The incidence of type 1 diabetes is rising worldwide, possibly owing to epigenetic and environmental factors. Globally in 2020 an estimated 8.7 million people were living with type 1 diabetes, of whom approximately 1.5 million were under 20 years of age.² This number is expected to rise to more than 17 million by 2040 (<https://www.t1dindex.org/#global>). The International Diabetes Federation estimates the global prevalence of type 1 diabetes

at 0.1%, and this is likely an underestimation as diagnoses of type 1 diabetes in adults are often not accounted for. The incidence of adult onset type 1 diabetes is higher in Europe, especially in Nordic countries, and lowest in Asian countries.³ Adult onset type 1 diabetes is also more prevalent in men than in women. An increase in prevalence in people under 20 years of age has been observed in several western cohorts including the US,^{4 5} Netherlands,⁶ Canada,⁷ Hungary,⁸ and Germany.⁹

Diagnosis

Classically, type 1 diabetes presents over the course of days or weeks in children and adolescents with polyuria, polydipsia, and weight loss due to glycosuria. The diagnosis is usually straightforward, with profound hyperglycemia (often >300 mg/dL) usually with ketonuria with or without ketoacidemia. Usually, more than one autoantibody is present at diagnosis (table 1).¹⁰ The number of islet autoantibodies combined with parameters of glucose tolerance now forms the basis of risk prediction for type 1 diabetes, with stage 3 being clinical disease (fig 1).¹¹ The originally discovered autoantibody, islet cell antibody, is no longer used clinically owing to variability of the assay despite standardisation.¹²

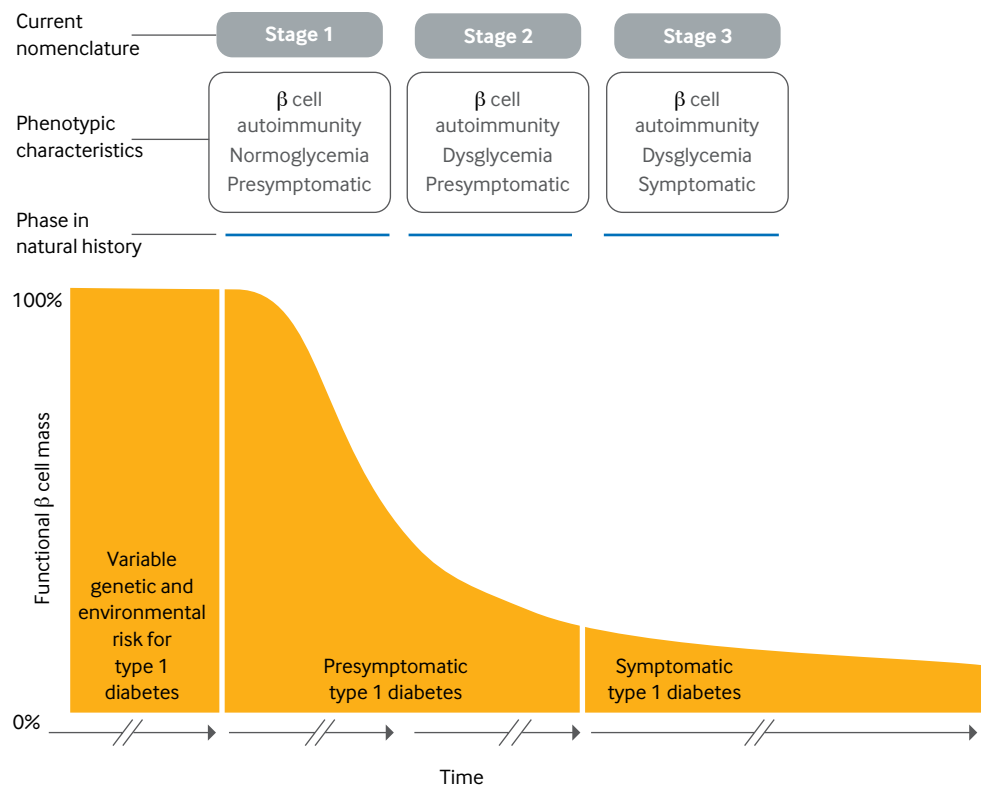


Fig 1 | Natural history of type 1 diabetes. Adapted with permission from Insel RA, et al. *Diabetes Care* 2015;38:1964-74¹¹

Half of all new cases of type 1 diabetes are now recognized as occurring in adults.¹³ Misclassification due to misdiagnosis (commonly as type 2 diabetes) occurs in nearly 40% of people.¹⁴ As opposed to typical childhood onset type 1 diabetes, progression to severe insulin deficiency, and therefore its clinical presentation in adults, is variable. The term latent autoimmune diabetes of adults (LADA) was introduced 30 years ago to identify adults who developed immune mediated diabetes.¹⁵ An international consensus defined the diagnostic criteria for LADA as age >30 years, lack of need for insulin use for at least six months, and presence of islet cell autoantibodies.¹⁶ However, debate as to whether the term LADA should even be used as a diagnostic term persists. The American Diabetes Association (ADA) Standards of Care note that for the purpose of classification, all forms of diabetes mediated by autoimmune β cell destruction are included in the classification of type 1 diabetes.¹⁷ Nevertheless, they note that use of the term

LADA is acceptable owing to the practical effect of heightening awareness of adults likely to have progressive autoimmune β cell destruction and thereby accelerating insulin initiation by clinicians to prevent diabetic ketoacidosis.

The investigation of adults with suspected type 1 diabetes is not always straightforward (fig 2).¹⁸ Islet cell autoantibodies such as glutamic acid decarboxylase antibody (GADA), tyrosine phosphatase IA2 antibody, and zinc transporter isoform 8 autoantibody act as markers of immune activity and can be detected in the blood with standardized assays (table 1). The presence of one or more antibodies in adults with diabetes could mark the progression to severe insulin deficiency; these individuals should be considered to have type 1 diabetes.¹ Autoantibodies, especially GADA, should be measured only in people with clinically suspected type 1 diabetes, as low concentrations of GADA can be seen in type 2 diabetes and thus false positive measurements are a concern.¹⁹ That

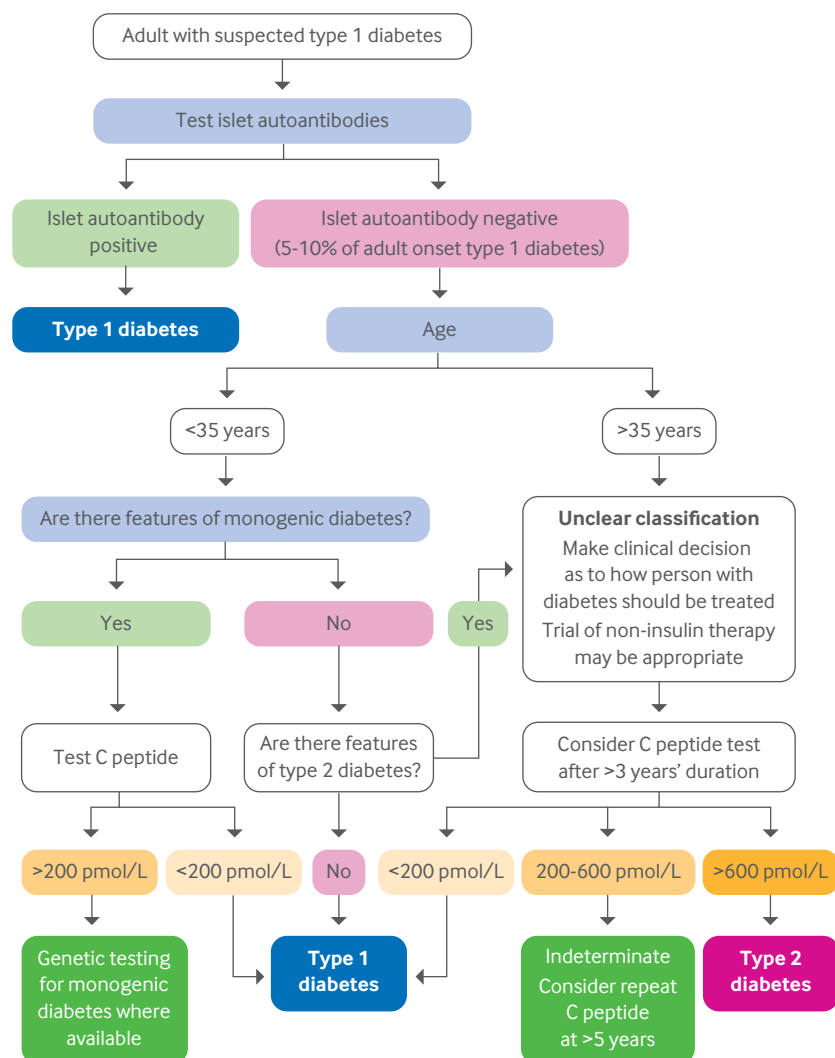


Fig 2 | Flowchart for investigation of suspected type 1 diabetes in adults, based on data from white European populations. No single clinical feature in isolation confirms type 1 diabetes. The most discriminative feature is younger age at diagnosis (<35 years), with lower body mass index (<25), unintentional weight loss, ketoacidosis, and glucose >360 mg/dL at presentation. Adapted with permission from Holt RIG, et al. *Diabetes Care* 2021;44:2589-625¹

5-10% of cases of type 1 diabetes may occur without diabetes autoantibodies is also now clear,²⁰ and that the diabetes autoantibodies disappear over time is also well appreciated.²¹

Genetic risk scoring (GRS) for type 1 diabetes has received attention to differentiate people whose classification is unclear.²²⁻²⁴ Developed in 2019, the T1D-GRS2 uses 67 single nucleotide polymorphisms from known autoimmune loci and can predict type 1 diabetes in children of European and African ancestry. Although GRS is not available for routine clinical use, it may allow prediction of future cases of type 1 diabetes to allow prevention strategies with immune intervention (see below).

A major change in the type 1 diabetes phenotype has occurred over the past few decades, with an increase in obesity; the reasons for this are complex. In the general population, including people with type 1 diabetes, an epidemic of sedentary lifestyles and the “westernized diet” consisting of increased processed foods, refined sugars, and saturated fat is occurring. In people with type 1 diabetes, the overall improvement in glycemic control since the report of the Diabetes Control and Complications Trial (DCCT) in 1993 (when one or two insulin injections a day was standard therapy) has resulted in less glycosuria so that the typical patient with lower body weight is uncommon in high income countries. In the US T1D Exchange, more than two thirds of the adult population were overweight or obese.²⁵

Similarly, obesity in young people with type 1 diabetes has also increased over the decades.²⁶ The combination of autoimmune insulin deficiency with obesity and insulin resistance has received several descriptive names over the years, with this phenotype being described as double diabetes and hybrid diabetes, among others,^{26 27} but no formal nomenclature in the diabetes classification exists. Many of these patients have family members with type 2 diabetes, and some patients probably do have both types of diabetes. Clinically, minimal research has been done into how this specific population responds to certain antihyperglycemic oral agents, such as glucagon-like peptide 1 (GLP-1) receptor agonists, given the glycemic, weight loss, and cardiovascular benefits seen with these agents.²⁸ These patients are common in most adult diabetes practices, and weight management in the presence of insulin resistance and insulin deficiency remains unclear.

Advances in monitoring

The introduction of home blood glucose monitoring (BGM) more than 45 years ago was met with much skepticism until the report of the DCCT.²⁹ Since then, home BGM has improved in accuracy, precision, and ease of use.³⁰ Today, in many parts of the world, home BGM, a static measurement of blood glucose, has been replaced by continuous glucose monitoring (CGM), a dynamic view of glycemia. CGM is superior to home BGM for glycemic control, as confirmed in a meta-analysis of 21 studies and 2149 participants with type 1 diabetes in which CGM

use significantly decreased glycated hemoglobin (HbA_{1c}) concentrations compared with BGM (mean difference -0.23%, 95% confidence interval -3.83 to -1.08; P<0.001), with a greater benefit if baseline HbA_{1c} was >8% (mean difference -0.43%, -6.04 to -3.30; P<0.001).³¹ This newer technology has also evolved into a critical component of automated insulin delivery.³²

CGM is the standard for glucose monitoring for most adults with type 1 diabetes.¹ This technology uses interstitial fluid glucose concentrations to estimate blood glucose. Two types of CGM are available. The first type, called “real time CGM”, provides a continuous stream of glucose data to a receiver, mobile application, smartwatch, or pump. The second type, “intermittently scanned CGM,” needs to be scanned by a reader device or smartphone. Both of these technologies have shown improvements in HbA_{1c} and amount of time spent in the hypoglycemic range compared with home BGM when used in conjunction with multiple daily injections or “open loop” insulin pump therapy.^{33 34} Real time CGM has also been shown to reduce hypoglycemic burden in older adults with type 1 diabetes (table 2).³⁶ Alerts that predict or alarm with both hypoglycemia and hyperglycemia can be customized for the patient’s situation (for example, a person with unawareness of hypoglycemia would have an alert at a higher glucose concentration). Family members can also remotely monitor glycemia and be alerted when appropriate. The accuracy of these devices has improved since their introduction in 2006, so that currently available sensors can be used without a confirmation glucose concentration to make a treatment decision with insulin. However, some situations require home BGM, especially when concerns exist that the CGM does not match symptoms of hypoglycemia.

Analysis of CGM reports retrospectively can assist therapeutic decision making both for the provider and the patient. Importantly, assessing the retrospective reports and watching the CGM in real time together offer insight to the patient with regard to insulin dosing, food choices, and exercise. Patients should be encouraged to assess their data on a regular basis to better understand their diabetes self-management. Table 3 shows standard metrics and targets for CGM data.⁵² Figure 3 shows an ambulatory glucose profile.

Improvements in technology and evidence for CGM resulting in international recommendations for its widespread use have resulted in greater uptake by people with type 1 diabetes across the globe where available and accessible. Despite this, not everyone wishes to use it; some people find wearing any device too intrusive, and for many the cost is prohibitive. These people need at the very least before meal and bedtime home BGM.

A next generation implantable CGM device (Sensonic), with an improved calibration algorithm that lasts 180 days after insertion by a healthcare professional, is available in both the EU and US. Although fingerstick glucose calibration is needed, the accuracy is comparable to that of other available devices.⁵³

Table 2 | Summary of trials for each topic covered

Study; author, year	Type of study; No of patients	Treatment and duration	Study endpoint/ primary outcome	Results
Continuous glucose monitoring				
DIAMOND; Beck RW et al, 2017 ³³	RCT; n=158, adults with T1D on multiple daily injections	Real time CGM v BGM with fingerstick testing; 24 weeks	Change in HbA _{1c} from baseline	Mean HbA _{1c} reduction from baseline was 1.0% at 24 weeks in CGM group and 0.4%, in BGM group (P<0.001)
GOLD; Lind M et al, 2017 ³⁵	Open label crossover RCT; n=161 adults with T1D on multiple daily injections	Real time CGM v BGM; 26 weeks, washout period of 17 weeks	Change in HbA _{1c} from baseline	Mean HbA _{1c} was 7.9% during CGM use and 8.4% during BGM use (mean difference -0.43% (95% CI -0.57% to -0.29%; P<0.001)
WISDM; Pratley RE et al, 2020 ³⁶	RCT; n=206, adults aged >60 with T1D on multiple daily injections or insulin pump	Real time CGM v BGM; 24 weeks	CGM measured percentage of time that sensor glucose values were <70 mg/dL during study	Median time with glucose values <70 mg/dL decreased from 5.1% (73 min/d) at baseline to 2.7% (39 min/d) during study in CGM group and from 4.7% (68 min/d) to 4.9% (70 min/d) in BGM group (adjusted treatment difference -1.9% (95% CI -2.8% to -1.1%) or -27 (-40 to -16) min/d; P<0.001)
FLASH-UK trial; Leelarathna L et al, 2022 ³⁴	RCT; n=156 adults with T1D on multiple daily injections or insulin pump	Intermittent scanned CGM v BGM; 24 weeks	Change in HbA _{1c} from baseline	Mean HbA _{1c} at baseline was 8.7% (SD 0.9%) in CGM group and 8.5% (0.8%) in BGM group. HbA _{1c} decreased to 7.9% (0.8%) and 8.3% (0.9%), respectively (adjusted mean between group difference -0.5, 95% CI -0.7 to -0.3; P<0.001). Time spent in target glucose range (70-180 mg/dL) was 9.0% (95% CI 4.7% to 13.3%) points higher and 130 (95% CI 68 to 192) min/d longer in CGM group than in BGM group; time spent in a hypoglycemic state (<70 mg/dL) was 3.0% (1.4% to 4.5%) points lower and 43 (20 to 65) min shorter in CGM group
Automated insulin delivery systems				
Tauschmann M et al, 2018 ³⁷	RCT; n=86 patients aged ≥6 with T1D on multiple daily injections or insulin pump	Open label, closed loop pump system v sensor augmented pump; 12 weeks	Percentage of time glucose value was within target range of 70-180 mg/dL on CGM	Glucose time within target range was higher in closed loop group (65% (SD 8%)) than in sensor augmented pump group (54% (9%)); mean difference in change 10.8% (95% CI 8.2% to 13.5%) points; P<0.0001). In closed loop group, HbA _{1c} decreased from 8.3% (SD 0.6%) to 7.4% (0.6%) after 12 weeks. In control group, HbA _{1c} values were 8.2% (0.5%) at screening and 7.7% (0.5%) after intervention (mean difference in change 0.36% (95% CI 0.19% to 0.53%); P<0.001)
Brown SA et al, 2019 ³²	RCT; n=168 adolescents and adults with T1D on multiple daily injections or insulin pump	Closed loop pump system v sensor augmented pump; 6 months	Percentage of time glucose value was within target range of 70-180 mg/dL on CGM	At study end, percentage time that glucose was within target range increased from 61% (SD 17%) at baseline to 71% (12%) in closed loop group and did not change at 59% (14%) in control group (mean adjusted difference 11 (95% CI 9 to 14) percentage points; P<0.001). Closed loop group had more adverse events due to hyperglycemia with ketosis from pump infusion set failure than control group
Bionic Pancreas Research Group, 2022 ³⁸	RCT; n=326 patients aged ≥6 with T1D on any insulin delivery method with CGM use	Insulin only bionic pancreas (n=219) v standard care (n=107); 13 weeks	Change in HbA _{1c} from baseline	HbA _{1c} decreased from 7.9% to 7.3% in bionic pancreas group and did not change (7.7% at beginning and end of study) in standard care group (mean adjusted difference at 13 weeks -0.5% (95% CI -0.6% to -0.3%); P<0.001). No difference in rate of severe hypoglycemia between groups (17.7 events/100 participant years in bionic pancreas group v 10.8 events/100 participant years in standard care group; P=0.39)
Insulin therapy, multiple daily injections				
SWITCH 1; Lane W et al, 2017 ³⁹	RCT; n=501 adults with T1D with ≥1 hypoglycemia risk factor	Open label, crossover, U100 glargine v degludec; 32 weeks + 32 weeks	Rate of hypoglycemia; non-inferiority trial	Rates of overall symptomatic hypoglycemia were 2200.9 episodes per 100 person years' exposure (PYE) in insulin degludec group v 2462.7 episodes per 100 PYE in insulin glargine U100 group; rate ratio 0.89 (95% CI 0.85 to 0.94); P<0.001 for non-inferiority; P<0.001 for superiority). Lower severe hypoglycemia rates in degludec arm
EDITION 4; Home PD, 2015 ⁴⁰	RCT; n=549 adults with T1D on multiple daily injections	Open label, U-100 glargine or U-300 glargine; 6 months	Change in HbA _{1c} from baseline, non-inferiority trial	Baseline HbA _{1c} was 8.1%. Change in HbA _{1c} was equivalent in the two insulin groups (difference 0.04%, 95% CI -0.10% to 0.19%), showing non-inferiority of Gla-300. Dose of Gla-300 required was higher but there was less severe hypoglycemia (rate ratio 0.69, 95% CI 0.53 to 0.91)
PRONTO-T1D; Klaff L et al, 2020 ⁴¹	RCT; n=1222 adults with T1D on multiple daily injections,	Mealtime ultra-rapid acting lispro URli (n=451), lispro (n=442), and post-meal URli (n=329)	Change in HbA _{1c} from baseline; non-inferiority trial	URli was non-inferior to lispro for HbA _{1c} reduction (-0.08%, 95% CI -0.16 to 0.00). Mealtime URli was superior to lispro in post-prandial glucose excursions and showed 37% lower hypoglycemia in period >4 h after meals (P=0.013)
ONSET 1; Mathieu C et al, 2018 ⁴²	RCT; n=761 adults with T1D on multiple daily injections	Mealtime faster aspart (n=381) v conventional aspart (n=380); 52 weeks	Change in HbA _{1c} from baseline; non-inferiority trial	Change in HbA _{1c} from baseline was -0.08% (faster aspart) and 0.01% (conventional aspart); estimated treatment difference significantly favored faster aspart (-0.10%, 95% CI -0.19 to 0.00; P=0.04). Faster aspart also improved postprandial glucose. No difference in hypoglycemia between groups
Immune therapies				
Herold KC et al, 2019 ⁴³	RCT; n=76 relatives of patients with T1D without diabetes but at high risk for development of clinical disease	Teplizumab 14 day course (n=44) v placebo (n=32); 4 years	Time to development of T1D	Median time to diagnosis of T1D was 48.4 months in the teplizumab group and 24.4 months in the placebo group (hazard ratio 0.41, 95% CI 0.22 to 0.78; P=0.006); T1D was diagnosed in 19/44 (43%) participants who received teplizumab and in 23/32 (72%) who received placebo. At the conclusion of the trial, 57% of people in the teplizumab group and 28% in the placebo group were diabetes-free. Rash and transient lymphopenia occurred in the treatment group
Adjuvant therapies: metformin				
Libman IM et al, 2015 ⁴⁴	RCT; n=140 adolescents with T1D	Metformin 2 g daily (n=71) v placebo (n=69); 26 weeks	Change in HbA _{1c} from baseline	Mean HbA _{1c} improved modestly at 13 weeks but was not sustained. At 26 weeks, change in HbA _{1c} from baseline was 0.2% in the metformin group and 0.2% in the placebo group (mean adjusted difference 0.0%, 95% CI -0.3% to 0.3%; P=0.92). However, total daily insulin dose/kg was lower in the metformin group (-0.1 U/kg per day) than in the placebo group (0.0 U/kg per day; mean difference -0.1, 95% CI -0.2 to -0.0; P<0.001)

(Continued)

Table 2 | Continued

Study; author, year	Type of study; No of patients	Treatment and duration	Study endpoint/primary outcome	Results
Petrie JR et al, 2017 ⁴⁵	RCT; n=428 adults with T1D	Metformin (n=219) v placebo (n=209); 36 months	Change in carotid intima-media thickness (cIMT)	Mean cIMT did not change from baseline in the metformin group (−0.005 (95% CI −0.012 to 0.002) mm/year; P=0.17); body weight (−1.17 (95% CI −1.66 to −0.69) kg; P<0.001) and LDL cholesterol (−0.13 (−0.24 to −0.03) mmol/L; P=0.01) decreased with metformin over 3 years
Adjuvant therapies: SGLT inhibitors				
DEPICT-1; Dandona P et al, 2018 ⁴⁶	RCT; n=833 adults with T1D on multiple daily injections	Dapagliflozin 5 mg (n=277), 10 mg (n=296) v placebo (n=260); 52 weeks	Change in HbA _{1c} from baseline	Both doses of dapagliflozin reduced HbA _{1c} (difference v placebo −0.33% (95% CI −0.49% to −0.17%) and −0.36% (−0.53% to −0.20%)) and body weight (difference v placebo −2.95% (−3.83% to −2.06%) and −4.54% (−5.40 to −3.66)). DKA events were increased in dapagliflozin groups
EASE-2 and 3; Rosenstock J et al, 2018 ⁴⁷	RCT; n=1707 adults with T1D	Empagliflozin 10 mg, 25 mg or placebo in EASE-2 (n=723); 52 weeks. 2.5 mg, 10 mg or 25 mg or placebo in EASE-3 (n=961); 26 weeks	Change in HbA _{1c} from baseline	Mean HbA _{1c} reduction after 26 weeks of empagliflozin was dose dependent (up to −0.54%; P<0.001). Empagliflozin 2.5 mg reduced HbA _{1c} (−0.28%; P<0.001). In EASE-2, body weight reduction (up to −3.4 kg; P<0.001), systolic blood pressure (up to −3.9 mm Hg; P<0.001), and diastolic blood pressure (up to −2.3 mm Hg; P<0.001). DKA rate in empagliflozin 2.5 mg group was similar to placebo (0.8% and 1.2%, respectively), but was higher in the empagliflozin 10 mg and 25 mg groups compared with placebo (4.3%, 3.3%, and 1.2%, respectively)
inTANDEM3; Garg SK et al, 2017 ⁴⁸	RCT; n=1402 adults with T1D on multiple daily injections or insulin pump	Sotagliflozin 400 mg (n=699), placebo (n=703); 24 weeks	Decrease in HbA _{1c} from baseline to <7%	A larger proportion of patients on sotagliflozin (200/699; 28.6%) than placebo (107/703; 15.2%) achieved the combined primary endpoint of HbA _{1c} <7.0% and no severe hypoglycemia or DKA at week 24. More patients on sotagliflozin than placebo achieved HbA _{1c} <7.0% (207 patients [29.6%] vs. 111 [15.8%]). There was no increase in hypoglycemia or DKA
Adjuvant therapies: GLP-1 receptor agonists				
ADJUNCT ONE; Mathieu C et al, 2016 ⁴⁹	RCT; n=1398 adults with T1D	Liraglutide v placebo added to multiple daily injections or insulin pump therapy; 52 weeks	Change in HbA _{1c} from baseline	Reduction in HbA _{1c} from baseline (8.1%) with liraglutide 1.8 mg and 1.2 mg v placebo (estimated treatment differences: 1.8 mg liraglutide −0.20%, 95% CI −0.32% to −0.07%; 1.2 mg liraglutide −0.15%, −0.27% to −0.03%). Mean body weight decreased in all liraglutide groups compared with placebo (estimated treatment differences 1.8 mg liraglutide −4.9 (95% CI −5.7 to −4.2) kg; 1.2 mg liraglutide −3.6 kg (−4.3 to −2.8) kg; 0.6 mg liraglutide −2.2 (−2.9 to −1.5) kg)
ADJUNCT TWO; Ahren B et al, 2016 ⁵⁰	RCT; n=835 adults with T1D	Liraglutide v placebo added to multiple daily injections or insulin pump therapy; 26 weeks	Change in HbA _{1c} from baseline	Liraglutide decreased HbA _{1c} v placebo (1.8 mg −0.33%; 1.2 mg −0.22%; 0.6 mg −0.23%; placebo 0.01%). Liraglutide reduced mean body weight (−5.1, −4.0, and −2.5 kg for 1.8, 1.2, and 0.6 mg, respectively) v placebo (−0.2 kg). Reduction in daily insulin dose and increases in quality of life with liraglutide; higher rates of symptomatic hypoglycemia (21.3 v 16.6 events/patient/year; P=0.03) and of hyperglycemia with ketosis >1.5 mmol/L with liraglutide 1.8 mg v placebo (0.5 v 0.1 events/patient/year; P=0.01)
Herold KC et al, 2020 ⁵¹	RCT; n=79 adults with T1D	Exenatide long acting v placebo added to multiple daily injections or insulin pump therapy; 24 weeks	Change in HbA _{1c} from baseline	Exenatide LAR treatment resulted in HbA _{1c} reduction to 7.76% (95% CI 7.42% to 8.10%) v placebo 8% (7.64% to 8.35%; P=0.08)

BGM=blood glucose monitoring; CGM=continuous glucose monitoring; CI=confidence interval; DKA=diabetic ketoacidosis; GLP-1=glucagon-like peptide 1; LDL=low density lipoprotein; RCT=randomized controlled trial; SGLT=sodium-glucose cotransporter; T1D=type 1 diabetes.

Advances in treatments

Insulins

The discovery of insulin in 1921, resulting in a Nobel Prize, was considered one of the greatest scientific achievements of the 20th century. The development of purified animal insulins in the late 1970s, followed by human insulin in the early 1980s, resulted in dramatic reductions in allergic reactions and lipoatrophy. Introduction of the first generation of insulin analogs, insulin lispro in the mid-1990s followed by insulin glargine in the early 2000s, was an important advance for the treatment of type 1 diabetes.⁵⁴ We review the next generation of insulin analogs here. Table 4 provides details on available insulins.

Ultra-long acting basal insulins

Insulin degludec was developed with the intention of improving the duration of action and achieving a flatter profile compared with the original long acting insulin analogs, insulin glargine and insulin detemir. Its duration of action of 42 hours at steady

state means that the profile is generally flat without significant day-to-day variability, resulting in less hypoglycemia compared with U-100 glargine.^{39 55}

When U-100 insulin glargine is concentrated threefold, its action is prolonged.⁵⁶ U-300 glargine has a different kinetic profile and is delivered in one third of the volume of U-100 glargine, with longer and flatter effects. The smaller volume of U-300 glargine results in slower and more gradual release of insulin monomers owing to reduced surface area in the subcutaneous space.⁵⁷ U-300 glargine also results in lesser hypoglycemia compared with U-100 glargine.⁵⁸

Ultra-rapid acting prandial insulins

Rapid acting insulin analogs include insulin lispro, aspart, and glulisine. With availability of insulin lispro, the hope was for a prandial insulin that better matched food absorption. However, these newer insulins are too slow to control the glucose spike seen with ingestion of a high carbohydrate load, leading to the development of insulins with even faster onset of action.

Table 3 | Standardized continuous glucose monitoring metrics for adults with diabetes⁵²

Metric	Target: most adults with type 1 diabetes	Target: older "high risk" individuals with type 1 diabetes
No of days sensor is worn	≥14 days	≥14 days
Glucose management indicator	<7%	Individualized
Time in range	<70%	>50%
Time below range <70 mg/dL (level 1 and level 2 hypoglycemia)	<4%	<1%
Time below range <54 mg/dL	<1%	<1%
Time above range >180 mg/dL	<25%	-
Time above range >250 mg/dL	<5%	<10%
Coefficient of variation	<36%*	<36%*

*No consensus on this value; lower number indicates lower risk of hypoglycemia.

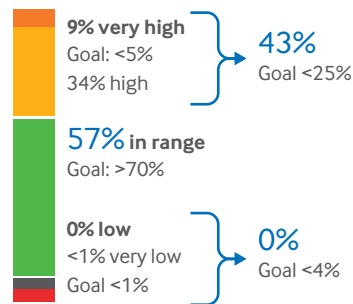
The first available ultra-rapid prandial insulin was fast acting insulin aspart. This insulin has an onset of appearance approximately twice as fast (~5 min earlier) as insulin aspart, whereas dose-concentration and dose-response relations are comparable between the two insulins (table 4).⁵⁹ In adults with type 1 diabetes, mealtime and post-meal fast acting aspart led to non-inferior glycemic control compared with mealtime aspart, in combination with basal insulin.⁶⁰ Mean HbA_{1c} was 7.3%, 7.3%, and 7.4% in the mealtime faster aspart, mealtime

aspart, and post-meal faster aspart arms, respectively (P<0.001 for non-inferiority).

Insulin lispro-aabc is the second ultra-rapid prandial insulin. In early kinetic studies, insulin lispro-aabc appeared in the serum five minutes faster with 6.4-fold greater exposure in the first 15 minutes compared with insulin lispro.⁶¹ The duration of exposure of the insulin concentrations in this study was 51 minutes faster with lispro-aabc. Overall insulin exposure was similar between the two groups. Clinically, lispro-aabc is non-inferior

Time in ranges Goals for type 1 and type 2 diabetes

Each 5% increase in the target range is clinically beneficial
Each 1% time in range = about 15 min/day



Target range: 70-180 mg/dL

Very high: >250 mg/dL

Very low: <54 mg/dL

Ambulatory glucose profile

Summary of glucose values from report period, with median (50%) and other centiles as if they occurred in a single day

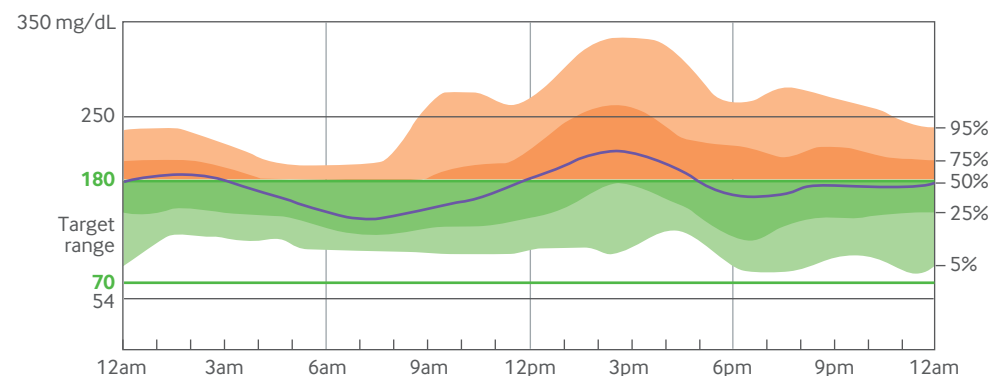


Fig 3 | Example of ambulatory glucose profile of 52 year old woman with type 1 diabetes and fear of hypoglycemia. CGM=continuous glucose monitoring; GMI=glucose management indicator

Table 4 | Pharmacokinetics of commonly used insulin preparations

	Half life*	Effective peak	Duration of action ²	Notes
Basal insulin type				
NPH	4.4 h	2-8 h	14-24 h	-
Insulin glargine U-100	12 h	No pronounced peak	20-24 h	-
Insulin glargine U-300	19 h	No pronounced peak	30-34 h	Higher doses by 10-20% compared with U-100 glargine will be needed
Detemir	5-7 h	3-9 h	8-24 h	-
Degludec	25 h	No pronounced peak	42 h	-
Prandial insulin type				
Human regular	30 min	2-4 h	5-8 h	Times vary depending on site of injection
Insulin lispro and aspart	15-30 min	1-3 h	4-7 h	-
Fast acting aspart	16-20 min	1-1.5 h	4-5 h	-
Lispro-aabc	15-17 min	1-1.5 h	4-5 h	More infusion site skin reactions than lispro
Inhaled insulin	12 min	0.5-0.9 h	1.5-3 h	Often requires postprandial dosing

NPH=neutral protamine Hagedorn.

*In general, four half lives are needed to reach steady state.

²In general, the larger the dose, the longer the duration of action.

to insulin lispro, but postprandial hyperglycemia is lower with the faster acting analog.⁶² Lispro-aabc given at mealtime resulted in greater improvement in post-prandial glucose (two hour post-prandial glucose -31.1 mg/dL, 95% confidence interval -41.0 to -21.2 ; $P<0.001$).

Both ultra-rapid acting insulins can be used in insulin pumps. Lispro-aabc tends to have more insertion site reactions than insulin lispro.⁶³ A meta-analysis including nine studies and 1156 participants reported increased infusion set changes on rapid acting insulin analogs (odds ratio 1.60, 95% confidence interval 1.26 to 2.03).⁶⁴

Pulmonary inhaled insulin

The quickest acting insulin is pulmonary inhaled insulin, with an onset of action of 12 minutes and a duration of 1.5-3 hours.⁶⁵ When used with postprandial supplemental dosing, glucose control is improved without an increase in hypoglycemia.⁶⁶

Insulin delivery systems

Approved automated insulin delivery systems

CGM systems and insulin pumps have shown improvement in glycemic control and decreased risk of severe hypoglycemia compared with use of self-monitoring of blood glucose and multiple daily insulin injections in type 1 diabetes.⁶⁷⁻⁶⁹ Using CGM and insulin pump together (referred to as sensor augmented pump therapy) only modestly improves HbA_{1c} in patients who have high sensor wear time,⁷⁰ but the management burden of diabetes does not decrease as frequent user input is necessary. Thus emerged the concept of glucose responsive automated insulin delivery (AID), in which data from CGM can inform and allow adjustment of insulin delivery.

In the past decade, exponential improvements in CGM technologies and refined insulin dosing pump algorithms have led to the development of AID systems that allow for minimization of insulin delivery burden. The early AID systems reduced hypoglycemia risk by automatically suspending insulin delivery when glucose concentrations dropped to below a pre-specified threshold but did

not account for high glucose concentrations. More complex algorithms adjusting insulin delivery up and down automatically in response to real time sensor glucose concentrations now allow close replication of normal endocrine pancreatic physiology.

AID systems (also called closed loop or artificial pancreas systems) include three components—an insulin pump that continuously delivers rapid acting insulin, a continuous glucose sensor that measures interstitial fluid glucose at frequent intervals, and a control algorithm that continuously adjusts insulin delivery that resides in the insulin pump or a smartphone application or handheld device (fig 4). All AID systems that are available today are referred to as “hybrid” closed loop (HCL) systems, as users are required to manually enter prandial insulin boluses and signal exercise, but insulin delivery is automated at night time and between meals. AID systems, regardless of the type used, have shown benefit in glycemic control and cost effectiveness, improve quality of life by improving sleep quality, and decrease anxiety and diabetes burden in adults and children.⁷²⁻⁷⁴ Limitations to today’s HCL systems are primarily related to pharmacokinetics and pharmacodynamics of available analog insulins and accuracy of CGM in extremes of blood glucose values. The iLet bionic pancreas, cleared by the US Food and Drug Administration (FDA) in May 2023, is an AID system that determines all therapeutic insulin doses for an individual on the basis of body weight, eliminating the need for calculation of basal rates, insulin to carbohydrate ratios, blood glucose corrections, and bolus dose. The control algorithms adapt continuously and autonomously to the individual’s insulin needs.³⁸ Table 5 lists available AID systems.

Unapproved systems

Do-it-yourself (DIY) closed loop systems—DIY open artificial pancreas systems—have been developed by people with type 1 diabetes with the goal of self-adjusting insulin by modifying their individually owned devices.⁷⁶ These systems are built by the individual using an open source code widely available to anyone with compatible medical devices

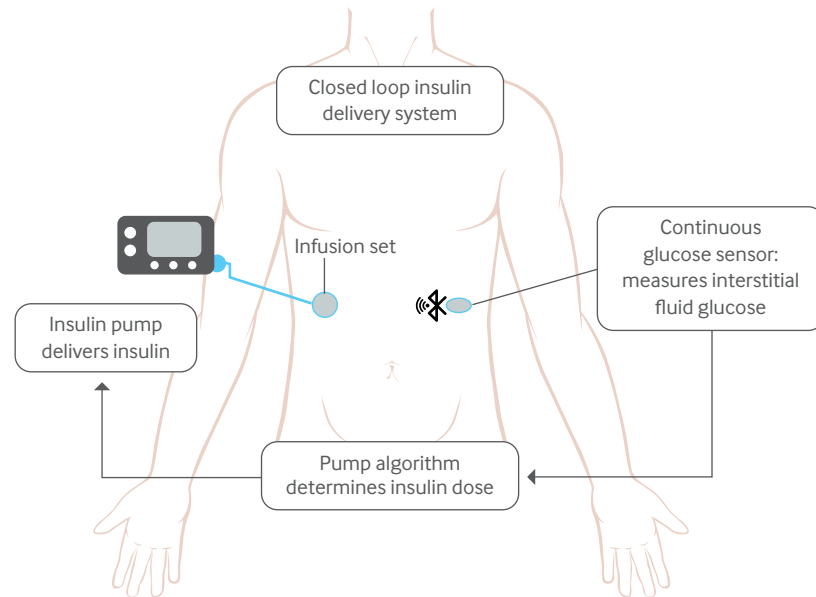


Fig 4 | Schematic of closed loop insulin pump technology. The continuous glucose monitor senses interstitial glucose concentrations and sends the information via Bluetooth to a control algorithm hosted on an insulin pump (or smartphone). The algorithm calculates the amount of insulin required, and the insulin pump delivers rapid acting insulin subcutaneously

who is willing and able to build their own system. DIY systems are used by several thousand people across the globe but are not approved by regulatory bodies; they are patient-driven and considered “off-label” use of technology with the patient assuming full responsibility for their use. Clinicians caring for these patients should ensure basic diabetes skills, including pump site maintenance, a knowledge of how the chosen system works, and knowing when to switch to “manual mode” for patients using an artificial pancreas system of any kind.⁷⁶ The small body of studies on DIY looping suggests improvement in HbA_{1c}, increased time in range, decreased hypoglycemia and glucose variability, improvement in night time blood glucose concentrations, and reduced mental burden of diabetes management.⁷⁷⁻⁷⁹ Although actively prescribing or initiating these options is not recommended, these patients should be supported by clinical teams; insulin prescription should not be withheld, and, if initiated by the patient, unregulated DIY options should be openly discussed to ensure open and transparent relationships.⁷⁸

In January 2023, the US FDA cleared the Tidepool Loop app, a DIY AID system. This software will connect the CGM, insulin pump, and Loop algorithm, but no RCTs using this method are available.

β cell replacement therapies

For patients with type 1 diabetes who meet specific clinical criteria, β cell replacement therapy using whole pancreas or pancreatic islet transplantation can be considered. Benefits of transplantation include immediate cessation of insulin therapy, attainment of euglycemia, and avoidance of hypoglycemia. Additional benefits include improved quality of life and stabilization of complications.⁸⁰ Chronic immunosuppression is needed to prevent graft rejection after transplantation.

Pancreas transplantation

Whole pancreas transplantation, first performed in 1966, involves complex abdominal surgery and lifelong immunosuppressive therapy and is limited by organ donor availability. Today, pancreas transplants are usually performed simultaneously

Table 5 | Comparison of commercially available hybrid closed loop systems⁷⁵

Variable	Medtronic 670G/780G AHCL	Tandem Control-IQ	CamAPS FX	Diabeloop DBLG1	Omnipod 5 HCL	iLet Betabionics
Licensed countries	USA, Canada, and Europe	USA, Canada, and Europe	Europe, Canada, and Australia	Europe	USA and Europe	USA
Algorithm location	Integrated in pump	Integrated in pump	App based	App based	Pod based	App based
Compatible CGM system	Guardian 3,4	Dexcom G6	Dexcom G6	Dexcom G6	Dexcom G6	Dexcom G6
Compatible insulin pump	Medtronic 670G or 780 G	T: Slim X2	Dana RS and Dana-i Ypso Pump	Accucheck Insight Kaleido	Omnipod	iLet
Type of algorithm	PID	MPC	MPC	MPC	MPC	MPC
Approved for ages	≥7 years	≥6 years	≥1 year	≥18 years	≥2 years	≥6 years

CGM=continuous glucose monitoring; MPC=model predictive control; PID=proportional integrative derivative.

using two organs from the same donor (simultaneous pancreas-kidney transplant (SPKT)), sequentially if the candidate has a living donor for renal transplantation (pancreas after kidney transplant (PAKT)) or on its own (pancreas transplantation alone). Most whole pancreas transplants are performed with kidney transplantation for end stage diabetic kidney disease. Pancreas graft survival at five years after SPKT is 80% and is superior to that with pancreas transplants alone (62%) or PAKT (67%).⁸¹ Studies from large centers where SPKT is performed show that recipients can expect metabolic improvements including amelioration of problematic hypoglycemia for at least five years.⁸¹ The number of pancreas transplantations has steadily decreased in the past two decades.

Islet transplantation

Islet transplantation can be pursued in selected patients with type 1 diabetes marked by unawareness of hypoglycemia and severe hypoglycemic episodes, to help restore the α cell response critical for responding to hypoglycemia.^{82,83} Islet transplantation involves donor pancreas procurement with subsequent steps to isolate, purify, culture, and infuse the islets. Multiple donors are needed to provide enough islet cells to overcome islet cell loss during transplantation. Survival of the islet grafts, limited donor supply, and lifelong need for immunosuppressant therapy remain some of the biggest challenges.⁸⁴ Islet transplantation remains experimental in the US and is offered in a few specialized centers in North America, some parts of Europe, and Australia.⁸⁵

Disease modifying treatments for β cell preservation

Therapies targeting T cells, B cells, and cytokines that find use in a variety of autoimmune diseases have also been applied to type 1 diabetes. The overarching goal of immune therapies in type 1 diabetes is to prevent or delay the loss of functional β cell mass. Studies thus far in early type 1 diabetes have not yet successfully shown reversal of loss of C peptide or maintenance of concentrations after diagnosis, although some have shown preservation or slowing of loss of β cells. This suggests that a critical time window of opportunity exists for starting treatment depending on the stage of type 1 diabetes (fig 1).

Teplizumab is a humanized monoclonal antibody against the CD3 molecule on T cells; it is thought to modify CD8 positive T lymphocytes, key effector cells that mediate β cell death and preserves regulatory T cells.⁸⁶ Teplizumab, when administered to patients with new onset of type 1 diabetes, was unable to restore glycemia despite C peptide preservation.⁸⁷ However, in its phase II prevention study of early intervention in susceptible individuals (at least two positive autoantibodies and an abnormal oral glucose tolerance test at trial entry), a single course of teplizumab delayed progression to clinical type 1 diabetes by about two years (table 2).⁴³ On the basis of

these results, teplizumab received approval in the US for people at high risk of type 1 diabetes in November 2022.⁸⁸ A phase III trial (PROTECT; NCT03875729) to evaluate the efficacy and safety of teplizumab versus placebo in children and adolescents with new diagnosis of type 1 diabetes (within six weeks) is ongoing.⁸⁹

Thus far, targeting various components of the immune response has been attempted in early type 1 diabetes without any long term beneficial effects on C peptide preservation. Co-stimulation blockade using CTLA4-Ig abatacept, a fusion protein that interferes with co-stimulation needed in the early phases of T cell activation that occurs in type 1 diabetes, is being tested for efficacy in prevention of type 1 diabetes (NCT01773707).⁹⁰ Similarly, several cytokine directed anti-inflammatory targets (interleukin 6 receptor, interleukin 1 β , tumor necrosis factor α) have not shown any benefit.

Non-immunomodulatory adjunctive therapies

Adjunctive therapies for type 1 diabetes have been long entertained owing to problems surrounding insulin delivery, adequacy of glycemic management, and side effects associated with insulin, especially weight gain and hypoglycemia. At least 50% of adults with type 1 diabetes are overweight or obese, presenting an unmet need for weight management in these people. Increased cardiovascular risk in these people despite good glycemic management presents additional challenges. Thus, use of adjuvant therapies may tackle these problems.

Metformin

Metformin, by decreasing hepatic glucose production, could potentially decrease fasting glucose concentrations.⁹¹ It has shown benefit in reducing insulin doses and possibly improving metabolic control in obese/overweight people with type 1 diabetes. A meta-analysis of 19 RCTs suggests short term improvement in HbA_{1c} that is not sustained after three months and is associated with higher incidence of gastrointestinal side effects.⁹² No evidence shows that metformin decreases cardiovascular morbidity in type 1 diabetes. Therefore, owing to lack of conclusive benefit, addition of metformin to treatment regimens is not recommended in consensus guidelines.

Glucagon-like peptide receptor agonists

Endogenous GLP-1 is an incretin hormone secreted from intestinal L cells in response to nutrient ingestion and enhances glucose induced insulin secretion, suppresses glucagon secretion, delays gastric emptying, and induces satiety.⁹³ GLP-1 promotes β cell proliferation and inhibits apoptosis, leading to expansion of β cell mass. GLP-1 secretion in patients with type 1 diabetes is similar to that seen in people without diabetes. Early RCTs of liraglutide in type 1 diabetes resulted in weight loss and modest lowering of HbA_{1c} (table 2).^{49,50} Liraglutide 1.8 mg in people with type 1 diabetes and higher body

mass index decreased HbA_{1c}, weight, and insulin requirements with no increased hypoglycemia risk.⁹⁴ However, on the basis of results from a study of weekly exenatide that showed similar results, these effects may not be sustained.⁵¹ A meta-analysis of 24 studies including 3377 participants showed that the average HbA_{1c} decrease from GLP-1 receptor agonists compared with placebo was highest for liraglutide 1.8 mg daily (−0.28%, 95% confidence interval −0.38% to −0.19%) and exenatide (−0.17%, −0.28% to 0.02%). The estimated weight loss from GLP-1 receptor agonists compared with placebo was −4.89 (−5.33 to −4.45) kg for liraglutide 1.8 mg and −4.06 (−5.33 to −2.79) kg for exenatide.⁹⁵ No increase in severe hypoglycemia was seen (odds ratio 0.67, 0.43 to 1.04) but therapy was associated with higher levels of nausea. GLP-1 receptor agonist use may be beneficial for weight loss and reducing insulin doses in a subset of patients with type 1 diabetes. GLP-1 receptor agonists are not a recommended treatment option in type 1 diabetes. Semaglutide is being studied in type 1 diabetes in two clinical trials (NCT05819138; NCT05822609).

Sodium-glucose cotransporter inhibitors

Sodium-glucose cotransporter 2 (SGLT-2), a protein expressed in the proximal convoluted tubule of the kidney, reabsorbs filtered glucose; its inhibition prevents glucose reabsorption in the tubule and increases glucose excretion by the kidney. Notably, the action of these agents is independent of insulin, so this class of drugs has potential as adjunctive therapy for type 1 diabetes. Clinical trials have shown significant benefit in cardiovascular and renal outcomes in type 2 diabetes; therefore, significant interest exists for use in type 1 diabetes. Several available SGLT-2 inhibitors have been studied in type 1 diabetes and have shown promising results with evidence of decreased total daily insulin dosage, improvement in HbA_{1c}, lower rates of hypoglycemia, and decrease in body weight; however, these effects do not seem to be sustained at one year in clinical trials and seem to wane with time. Despite beneficial effects, increased incidence of diabetic ketoacidosis has been observed in all trials, is a major concern, and is persistent despite educational efforts.⁹⁶⁻⁹⁸ Low dose empagliflozin (2.5 mg) has shown lower rates of diabetic ketoacidosis in clinical trials (table 2).⁴⁷ Favorable risk profiles have been noted in Japan, the only market where SGLT-2 inhibitors are approved for adjunctive use in type 1 diabetes.⁹⁹ In the US, SGLT-2 inhibitors are approved for use in type 2 diabetes only. In Europe, although dapagliflozin was approved for use as adjunct therapy to insulin in adults with type 1 diabetes, the manufacturer voluntarily withdrew the indication for the drug in 2021.¹⁰⁰ Sotagliflozin is a dual SGLT-1 and SGLT-2 inhibitor that decreases renal glucose reabsorption through systemic inhibition of SGLT-2 and decreases glucose absorption in the proximal intestine by SGLT-1 inhibition, blunting and delaying postprandial hyperglycemia.¹⁰¹ Studies of sotagliflozin in type 1 diabetes have

shown sustained HbA_{1c} reduction, weight loss, lower insulin requirements, lesser hypoglycemia, and more diabetic ketoacidosis relative to placebo.¹⁰²⁻¹⁰⁴ The drug received authorization in the EU for use in type 1 diabetes, but it is not marketed there. Although SGLT inhibitors are efficacious in type 1 diabetes management, the risk of diabetic ketoacidosis is a major limitation to widespread use of these agents.

Updates in acute complications of type 1 diabetes **Diabetic ketoacidosis**

Diabetic ketoacidosis is a serious and potentially fatal hyperglycemic emergency accompanied by significant rates of mortality and morbidity as well as high financial burden for healthcare systems and societies. In the past decade, increasing rates of diabetic ketoacidosis in adults have been observed in the US and Europe.^{105 106} This may be related to changes in the definition of diabetic ketoacidosis, use of medications associated with higher risk, and admission of patients at lower risk.¹⁰⁷ In a US report of hospital admissions with diabetic ketoacidosis, 53% of those admitted were between the ages of 18 and 44, with higher rates in men than in women.¹⁰⁸ Overall, although mortality from diabetic ketoacidosis in developed countries remains low, rates have risen in people aged >60 and in those with coexisting life threatening illnesses.^{109 110} Recurrent diabetic ketoacidosis is associated with a substantial mortality rate.¹¹¹ Frequency of diabetic ketoacidosis increases with higher HbA_{1c} concentrations and with lower socioeconomic status.¹¹² Common precipitating factors include newly diagnosed type 1 diabetes, infection, poor adherence to insulin, and an acute cardiovascular event.¹⁰⁹

Euglycemic diabetic ketoacidosis refers to the clinical picture of an increased anion gap metabolic acidosis, ketonemia, or significant ketonuria in a person with diabetes without significant glucose elevation. This can be seen with concomitant use of SGLT-2 inhibitors (currently not indicated in type 1 diabetes), heavy alcohol use, cocaine use, pancreatitis, sepsis, and chronic liver disease and in pregnancy.¹¹³ Treatment is similar to that for hyperglycemic diabetic ketoacidosis but can require earlier use and greater concentrations of a dextrose containing fluid for the insulin infusion in addition to 0.9% normal saline resuscitation fluid.¹¹⁴

The diagnosis of diabetic ketoacidosis has evolved from a gluco-centric diagnosis to one requiring hyperketonemia. By definition, independent of blood glucose, a β-hydroxybutyrate concentration >3 mmol/L is required for diagnosis.¹¹⁵ However, the use of this ketone for assessment of the severity of the diabetic ketoacidosis is controversial.¹¹⁶ Bedside β-hydroxybutyrate testing during treatment is standard of care in many parts of the world (such as the UK) but not others (such as the US). Concerns have been raised about accuracy of bedside β-hydroxybutyrate meters, but this is related to concentrations above the threshold for diabetic ketoacidosis.¹¹⁶

Goals for management of diabetic ketoacidosis include restoration of circulatory volume, correction of electrolyte imbalances, and treatment of hyperglycemia. Intravenous regular insulin infusion is the standard of care for treatment worldwide owing to rapidity of onset of action and rapid resolution of ketonemia and hyperglycemia. As hypoglycemia and hypokalemia are more common during treatment, insulin doses are now recommended to be reduced from 0.1 u/kg/h to 0.05 u/kg/h when glucose concentrations drop below 250 mg/dL or 14 mM.¹¹⁵ Subcutaneous rapid acting insulin protocols have emerged as alternative treatments for mild to moderate diabetic ketoacidosis.¹¹⁷ Such regimens seem to be safe and have the advantages of not requiring admission to intensive care, having lower rates of complications related to intravenous therapy, and requiring fewer resources.^{117 118} Ketonemia and acidosis resolve within 24 hours in most people.¹¹⁵ To prevent rebound hyperglycemia, the transition off an intravenous insulin drip must overlap subcutaneous insulin by at least two to four hours.¹¹⁵

Hypoglycemia

Hypoglycemia, a common occurrence in people with type 1 diabetes, is a well appreciated effect of insulin treatment and occurs when blood glucose falls below the normal range. Increased susceptibility to hypoglycemia from exogenous insulin use in people with type 1 diabetes results from multiple factors, including imperfect subcutaneous insulin delivery tools, loss of glucagon within a few years of diagnosis, progressive impairment of the sympatho-adrenal response with repeated hypoglycemic episodes, and eventual development of impaired awareness. In 2017 the International Hypoglycemia Study Group developed guidance for definitions of hypoglycemia; on the basis of this, a glucose concentration of 3.0–3.9 mmol/L (54–70 mg/dL) was designated as level 1 hypoglycemia, signifying impending development of level 2 hypoglycemia—a glucose concentration <3 mmol/L (54 mg/dL).^{119 120} At approximately 54 mg/dL, neuroglycopenic hypoglycemia symptoms, including vision and behavior changes, seizures, and loss of consciousness, begin to occur as a result of glucose deprivation of neurons in the central nervous system. This can eventually lead to cerebral dysfunction at concentrations <50 mg/dL.¹²¹ Severe hypoglycemia (level 3), denoting severe cognitive and/or physical impairment and needing external assistance for recovery, is a common reason for emergency department visits and is more likely to occur in people with lower socioeconomic status and with the longest duration of diabetes.¹¹² Prevalence of self-reported severe hypoglycemia is very high according to a global population study that included more than 8000 people with type 1 diabetes.¹²² Severe hypoglycemia occurred commonly in younger people with suboptimal glycemia according to a large electronic health record database study in the US.¹²³ Self-reported severe hypoglycemia is associated with a 3.4-fold increase in mortality.^{124 125}

Acute consequences of hypoglycemia include impaired cognitive function, temporary focal deficits including stroke-like symptoms, and memory deficits.¹²⁶ Cardiovascular effects including tachycardia, arrhythmias, QT prolongation, and bradycardia can occur.¹²⁷ Hypoglycemia can impair many activities of daily living, including motor vehicle safety.¹²⁸ In a survey of adults with type 1 diabetes who drive a vehicle at least once a week, 72% of respondents reported having hypoglycemia while driving, with around 5% reporting a motor vehicle accident due to hypoglycemia in the previous two years.¹²⁹ This contributes to the stress and fear that many patients face while grappling with the difficulties of ongoing hypoglycemia.¹³⁰

Glucagon is highly efficacious for the primary treatment of severe hypoglycemia when a patient is unable to ingest carbohydrate safely, but it is unfortunately under-prescribed and underused.¹³¹ Availability of nasal, ready to inject, and shelf-stable liquid glucagon formulations have superseded the need for reconstituting older injectable glucagon preparations before administration and are now preferred.^{133 134} Real time CGM studies have shown a decreased hypoglycemic exposure in people with impaired awareness without a change in HbA_{1c}.^{34 135–138} CGM has shown benefit in decreasing hypoglycemia across the lifespan, including in teens, young adults, and older people.^{36 139} Although CGM reduces the burden of hypoglycemia including severe hypoglycemia, it does not eliminate it; overall, such severe level 3 hypoglycemia rates in clinical trials are very low and hard to decipher in the real world. HCL insulin delivery systems integrated with CGM have been shown to decrease hypoglycemia. Among available rapid acting insulins, ultra-rapid acting lispro (lispro-aabc) seems to be associated with less frequent hypoglycemia in type 1 diabetes.^{140 141}

As prevention of hypoglycemia is a crucial aspect of diabetes management, formal training programs to increase awareness and education on avoidance of hypoglycemia, such as the UK's Dose Adjustment for Normal Eating (DAFNE), have been developed.^{142 143} This program has shown fewer severe hypoglycemia (mean 1.7 (standard deviation 8.5) episodes per person per year before training to 0.6 (3.7) episodes one year after training) and restoration of recognition of hypoglycemia in 43% of people reporting unawareness. Clinically relevant anxiety and depression fell from 24.4% to 18.0% and from 20.9% to 15.5%, respectively. A structured education program with cognitive and psychotherapeutic aspects for changing hypoglycemia related behaviors, called the Hypoglycemia Awareness Restoration Program despite optimized self-care (HARPro), showed a positive effect on changing unhelpful beliefs around hypoglycemia and improved diabetes related and general distress and anxiety scores.¹⁴⁴

Management in under-resourced settings

According to a recent estimate from the International Diabetes Federation, 1.8 million people with type

1 diabetes live in low and middle income countries (LMICs).² In many LMICs, the actual burden of type 1 diabetes remains unknown and material resources needed to manage type 1 diabetes are lacking.^{145 146} Health systems in these settings are underequipped to tackle the complex chronic disease that is type 1 diabetes. Few diabetes and endocrinology specialist physicians are available owing to lack of specific postgraduate training programs in many LMICs; general practitioners with little to no clinical experience in managing type 1 diabetes care for these patients.¹⁴⁶ This, along with poor availability and affordability of insulin and lack of access to technology, results in high mortality rates.¹⁴⁷⁻¹⁴⁹ In developed nations, low socioeconomic status is associated with higher levels of mortality and morbidity for adults with type 1 diabetes despite access to a universal healthcare system.¹⁵⁰ Although global governments have committed to universal health coverage and therefore widespread availability of insulin, it remains very far from realization in most LMICs.¹⁵¹

Access to technology is patchy and varies globally. In the UST1DX, CGM use was least in the lowest fifth of socioeconomic status.¹⁵² Even where technology is available, successful engagement does not always occur.¹⁵³ In a US cohort, lower CGM use was seen in non-Hispanic Black children owing to lower rates of device initiation and higher rates of discontinuation.¹⁵⁴ In many LMICs, blood glucose testing strips are not readily available and cost more than insulin.¹⁵¹ In resource limited settings, where even diagnosis, basic treatments including insulin, syringes, and diabetes education are limited, use of CGM adds additional burden to patients. Need for support services and the time/resources needed to download and interpret data are limiting factors from a clinician's perspective. Current rates of CGM use in many LMICs are unknown.

Inequities in the availability of and access to certain insulin formulations continue to plague diabetes care.¹⁵⁵ In developed countries such as the US, rising costs have led to insulin rationing by around 25% of people with type 1 diabetes.¹⁵⁶ LMICs have similar trends while also remaining burdened by disproportionate mortality and complications from type 1 diabetes.^{155 157} With the inclusion of long acting insulin analogs in the World Health Organization's Model List of Essential Medicines in 2021, hope has arisen that these will be included as standard of care across the world.¹⁵⁸ In the past, the pricing of long acting analogs has limited their use in resource poor settings¹⁵⁹; however, their inclusion in WHO's list was a major step in improving their affordability.¹⁵⁸ With the introduction of lower cost long acting insulin biosimilars, improved access to these worldwide in the future can be anticipated.¹⁶⁰

Making insulin available is not enough on its own to improve the prognosis for patients with diabetes in resource poor settings.¹⁶¹ Improved healthcare infrastructure, better availability of diabetes supplies, and trained personnel are all critical to improving

type 1 diabetes care in LMICs.¹⁶¹ Despite awareness of limitations and barriers, a clear understanding of how to implement management strategies in these settings is still lacking. The Global Diabetes Compact was launched in 2021 with the goal of increasing access to treatment and improving outcomes for people with diabetes across the globe.¹⁶²

Emerging technologies and treatments

Monitoring systems

The ability to measure urinary or more recently blood ketone concentrations is an integral part of self-management of type 1 diabetes, especially during acute illness, intermittent fasting, and religious fasts to prevent diabetic ketoacidosis.¹⁶³ Many people with type 1 diabetes do not adhere to urine or blood ketone testing, which likely results in unnecessary episodes of diabetic ketoacidosis.¹⁶⁴ Noting that blood and urine ketone testing is not widely available in all countries and settings is important.¹ Regular assessment of patients' access to ketone testing (blood or urine) is critical for all clinicians. Euglycemic diabetic ketoacidosis in type 1 diabetes is a particular problem with concomitant use of SGLT-2 inhibitors; for this reason, these agents are not approved for use in these patients. For sick day management (and possibly for the future use of SGLT-2 inhibitors in people with type 1 diabetes), it is hoped that continuous ketone monitoring (CKM) can mitigate the risks of diabetic ketoacidosis.¹⁶⁵ Like CGM, the initial CKM device measures interstitial fluid β -hydroxybutyrate instead of glucose. CKM use becomes important in conjunction with a hybrid closed loop insulin pump system and added SGLT-2 inhibitor therapy, where insulin interruptions are common and hyperketonemia is frequent.¹⁶⁶

Perhaps the greatest technological challenge to date has been the development of non-invasive glucose monitoring. Numerous attempts have been made using strategies including optics, microwave, and electrochemistry.¹⁶⁷ Lack of success to date has resulted in healthy skepticism from the medical community.¹⁶⁸ However, active interest in the development of non-invasive technology with either interstitial or blood glucose remains.

Insulin and delivery systems

In the immediate future, two weekly basal insulins, insulin icodec and basal insulin Fc, may become available.¹⁶⁹ Studies of insulin icodec in type 1 diabetes are ongoing (ONWARDS 6; NCT04848480). How these insulins will be incorporated in management of type 1 diabetes is not yet clear.

Currently available AID systems use only a single hormone, insulin. Dual hormone AID systems incorporating glucagon are in development.^{170 171} Barriers to the use of dual hormone systems include the need for a second chamber in the pump, a lack of stable glucagon formulations approved for long term subcutaneous delivery, lack of demonstrated long term safety, and gastrointestinal side effects from glucagon use.⁷⁴ Similarly, co-formulations of insulin

Table 6 | Guidelines in type 1 diabetes

Area of interest in T1D	Available guidelines or consensus statements	Year
Diagnosis	Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023, American Diabetes Association ¹⁷	2023
	Management of Latent Autoimmune Diabetes in Adults: A Consensus Statement From an International Expert Panel ¹⁷⁷	2020
Management of T1D	The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) ¹	2021
	Diabetes Canada Clinical Practice Guidelines Expert Committee: Glycemic Management in Adults With Type 1 Diabetes ¹⁷⁸	2018
	National Institute for Health and Care Excellence (UK). Type 1 diabetes in adults: diagnosis and management (https://www.nice.org.uk/guidance/ng17)	2015
Technology	International Consensus on Use of Continuous Glucose Monitoring ⁹⁶	2017
Insulin pump therapy	Insulin pump risks and benefits: a clinical appraisal of pump safety standards, adverse event reporting and research needs. A Joint Statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group ¹⁷⁹	2015
Automated insulin delivery	Automated insulin delivery: benefits, challenges, and recommendations. A Consensus Report of the Joint Diabetes Technology Working Group of the European Association for the Study of Diabetes and the American Diabetes Association ¹⁸⁰	2022
	Consensus Recommendations for the Use of Automated Insulin Delivery Technologies in Clinical Practice ¹⁸¹	2023
Diabetic ketoacidosis	Position statement: The management of diabetic ketoacidosis in adults—An updated guideline from the Joint British Diabetes Society for Inpatient Care ¹¹⁵	2022
Hypoglycemia	Management of Individuals With Diabetes at High Risk for Hypoglycemia: An Endocrine Society Clinical Practice Guideline ¹⁸²	2023

T1D=type 1 diabetes.

and amylin (a hormone co-secreted with insulin and deficient in people with type 1 diabetes) are in development.¹⁷²

Immunotherapy for type 1 diabetes

As our understanding of the immunology of type 1 diabetes expands, development of the next generation of immunotherapies is under active pursuit. Antigen specific therapies, peptide immunotherapy, immune tolerance using DNA vaccination, and regulatory T cell based adoptive transfer targeting β cell senescence are all future opportunities for drug development. Combining immunotherapies with metabolic therapies such as GLP-1 receptor agonists to help to improve β cell mass is being actively investigated.

β cell replacement therapies

The quest for β cell replacement methods is ongoing. Transplantation of stem cell derived islets offers promise for personalized regenerative therapies as a potentially curative method that does away with the need for donor tissue. Since the first in vivo model of glucose responsive β cells derived from human embryonic stem cells,¹⁷³ different approaches have been attempted. Mesenchymal stromal cell treatment and autologous hematopoietic stem cells in newly diagnosed type 1 diabetes may preserve β cell function without any safety signals.¹⁷⁴⁻¹⁷⁶ Stem cell transplantation for type 1 diabetes remains investigational. Encapsulation, in which β cells are protected using a physical barrier to prevent immune attack and avoid lifelong immunosuppression, and gene therapy techniques using CRISPR technology also remain in early stages of investigation.

Guidelines

Until recently, no specific guidelines for management of type 1 diabetes existed and management guidance was combined with consensus statements developed for type 2 diabetes. Table 6 summarizes available guidance and statements from various societies. A consensus report for management of type 1 diabetes

in adults by the ADA and European Association for the Study of Diabetes became available in 2021; it covers several topics of diagnosis and management of type 1 diabetes, including glucose monitoring, insulin therapy, and acute complications. Similarly, the National Institute for Health and Care Excellence also offers guidance on management of various aspects of type 1 diabetes. Consensus statements for use of CGM, insulin pump, and AID systems are also available.

Conclusions

Type 1 diabetes is a complex chronic condition with increasing worldwide prevalence affecting several million people. Several successes in management of type 1 diabetes have occurred over the years from the serendipitous discovery of insulin in 1921 to blood glucose monitoring, insulin pumps, transplantation, and immunomodulation. The past two decades have seen advancements in diagnosis,

GLOSSARY OF ABBREVIATIONS

- ADA—American Diabetes Association
- AID—automated insulin delivery
- BGM—blood glucose monitoring
- CGM—continuous glucose monitoring
- CKM—continuous ketone monitoring
- DCCT—Diabetes Control and Complications Trial
- DIY—do-it-yourself
- FDA—Food and Drug Administration
- GADA—glutamic acid decarboxylase antibody
- GLP-1—glucagon-like peptide 1
- GRS—genetic risk scoring
- HbA_{1c}—glycated hemoglobin
- HCL—hybrid closed loop
- LADA—latent autoimmune diabetes of adults
- LMIC—low and middle income country
- PAKT—pancreas after kidney transplant
- RCT—randomized controlled trial
- SGLT-2—sodium-glucose cotransporter 2
- SPKT—simultaneous pancreas-kidney transplant

QUESTIONS FOR FUTURE RESEARCH

- What future new technologies can be helpful in management of type 1 diabetes?
- How can newer insulin delivery methods benefit people with type 1 diabetes?
- What is the role of disease modifying treatments in prevention and delay of type 1 diabetes?
- Is there a role for sodium-glucose co-transporter inhibitors or glucagon-like peptide 1 receptor antagonists in the management of type 1 diabetes?
- As the population with type 1 diabetes ages, how should management of these people be tailored?
- How can we better serve people with type 1 diabetes who live in under-resourced settings with limited access to medications and technology?

treatment, and technology including development of analog insulins, CGM, and advanced insulin delivery systems. Although we have gained a broad understanding on many important aspects of type 1 diabetes, gaps still exist. Pivotal research continues targeting immune targets to prevent or delay onset of type 1 diabetes. Although insulin is likely the oldest of existing modern drugs, no low priced generic supply of insulin exists anywhere in the world. Management of type 1 diabetes in under resourced areas continues to be a multifaceted problem with social, cultural, and political barriers.

How patients were involved in the creation of this manuscript

A person with lived experience of type 1 diabetes reviewed a draft of the manuscript and offered input on important aspects of their experience that should be included. This person is involved in large scale education and activism around type 1 diabetes. They offered their views on various aspects of type 1 diabetes, especially the use of adjuvant therapies and the burden of living with diabetes. This person also raised the importance of education of general practitioners on the various stages of type 1 diabetes and the management aspects. On the basis of this feedback, we have highlighted the burden of living with diabetes on a daily basis.

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