A perspective on treating type 1 diabetes mellitus before insulin is needed

Danijela Tatovic 1 , Parth Narendran 2 & Colin M. Dayan 1

1 Diabetes Research Group, Division of Infection and Immunity, Cardiff University School of Medicine, Cardiff, UK. 2 Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK. e-mail: dayancm@cardiff.ac.uk

Abstract

Type 1 diabetes mellitus (T1DM) is a progressive autoimmune disease that starts long before a clinical diagnosis is made. The American Diabetes Association recognizes three stages: stage 1 (normoglycaemic and positive for autoantibodies to β-cell antigens); stage 2 (asymptomatic with dysglycaemia); and stage 3, which is defned by glucose levels consistent with the defnition of diabetes mellitus. This Perspective focuses on the management of the proportion of individuals with early stage 3 T1DM who do not immediately require insulin; a stage we propose should be termed stage 3a. To date, this period of non-insulin-dependent T1DM has been largely unrecognized. Importantly, it represents a window of opportunity for intervention, as remaining at this stage might delay the need for insulin by months or years. Extending the insulin-free period and/or avoiding unnecessary insulin therapy are important goals, as there is no risk of hypoglycaemia during this period and the adherence burden on patients of glycaemic monitoring and daily adjustments for diet and exercise is substantially reduced. Recognizing the pressing need for guidance on adequate management of children and adults with stage 3a T1DM, we present our perspective on the subject, which needs to be tested in formal and adequately powered clinical trials.

Introduction

Type 1 diabetes mellitus (T1DM) is caused by autoimmune-mediated destruction of the pancreatic β-cells. The disease process starts long before a clinical diagnosis is made and progresses to dependence on exogenous insulin with absolute or near-absolute insulin deficiency1–4 . Replacement insulin therapy has been the mainstay of T1DM treatment ever since the introduction of insulin into clinical care over 100 years ago5–8 . Despite advances in insulin delivery methods, most people with T1DM (>70%) do not achieve optimal glycaemic control with this approach9–14. T1DM is often referred to as ‘insulin-dependent diabetes mellitus’ and the association between T1DM and the need for insulin for survival (irrespective of the stage of the autoimmune process, β-cell reserve and level of glycaemic control) is ingrained in the mind of many clinicians. Therefore, insulin is often started as soon as autoimmunemediated diabetes mellitus is suspected. However, the start of insulin injections is a major life-changing event for the individual and the individual’s family, and as such must be appropriate and timely. We now have a better understanding of the dynamics of the autoimmune process and have means of assessing endogenous insulin production in a simple and non-invasive way in the clinical setting by measuring C-peptide levels15,16. It is therefore increasingly being recognized that there is a period of ‘non-insulin-requiring T1DM’ that might include a period early after hyperglycaemia develops, but when the endogenous insulin production remains sufficient to enable optimal glycaemic control16. Currently, patients in this stage of the disease process are largely diagnosed in the research setting. However, this cohort of patients is likely to increase in size with the advent of screening programmes for early T1DM and with the progress in disease modifying therapies that have the potential to change the course of the autoimmune

process. The ultimate ambition of immune intervention in T1DM is preserving β-cell function to a level such that at-risk individuals do not require insulin replacement throughout their life. The latest FDA approval of teplizumab for use in stage 2 of T1DM represents a groundbreaking advance in fulfilling this goal17. However, it is realistic to expect that even with screening and availability of immunomodulation for all at-risk individuals, there will be a considerable proportion of people who will still progress to the later stages of T1DM. For some of these patients, reducing the length of time they are dependent on exogenous insulin, rather than aiming for lifelong insulin-free status, is a more realistic goal. It is therefore timely to consider revising our current management strategy for T1DM, with a focus on the level of β-cell preservation and delaying the introduction of insulin until it is required.

Box 1

Hypothetical clinical case scenarios

Hypothetical clinical case 1
A 28-year-old man with a BMI of 25 kg/m^2 and no family history of diabetes mellitus attends an insurance medical. He has no symptoms and his weight is stable. His HbA_{1c} measurement was found to be 51 mmol/mol (6.8%). β-Cell autoantibody testing was positive for anti-GAD at high titre. Random (non-fasting) C-peptide was 913 pmol/l.

Hypothetical clinical case 2
A 9-year-old girl is tested for β-cell autoantibodies as her brother and mother both have type 1 diabetes mellitus. She has no symptoms. She was found to be positive for anti-GAD and anti-ZnT8 and her HbA_{1c} was 50 mmol/mol (6.7%). Random (non-fasting) C-peptide was 840 pmol/l.

Conclusions
Both of these individuals are in the early stage of autoimmune type 1 diabetes mellitus, but have considerable endogenous insulin production that keeps them symptom-free and provides them with good glycaemic control that does not represent a high risk of microvascular complications.

Defining stage 3a T1DM

Three stages of T1DM have been defined and are now recognized by the American Diabetes Association (ADA) and the International Society of Paediatric and Adolescent Diabetes18,19. In stage 1, individuals are normoglycaemic, but are positive for two or more autoantibodies to β-cell antigens, which indicates that the autoimmune process is underway and that the individual has a >90% chance of progressing to insulin dependence over time20,21. This stage is followed by stage 2, where the still-asymptomatic individuals develop dysglycaemia with an estimated 5-year risk of progressing to T1DM of approximately 75%21. Stage 3 is defined by glucose levels consistent with the ADA

definition of diabetes mellitus, which indicates that individuals now have a level of chronic hyperglycaemia that puts them at risk of microvascular complications in the long term19.

The first presentation of T1DM in almost all individuals has been with clinical symptoms (for example, weight loss, polydipsia and polyuria), markedly raised glucose levels and, in >25% of individuals, established ketoacidosis22–24. We now recognize that this presentation represents a fairly late stage in the autoimmune process, when an estimated 80% or more of β-cells have ceased to function or have been destroyed25. However, with increased awareness of the natural history of the autoimmune process and the clinical availability of β-cell autoantibody assays (for example, anti-insulin, anti-GAD, anti-IA2 and anti-ZnT8)26–30, an increasing number of adults and children are being diagnosed at an earlier stage.

Currently, an earlier diagnosis is most common in young adults in whom autoantibody tests have been performed to distinguish T1DM from type 2 diabetes mellitus (T2DM) or in whom raised glucose levels and positivity for antibodies are identified on routine HbA1c screening for T2DM (clinical case scenario 1 in Box 1). With the gradual introduction of autoantibody screening in relatives of people with T1DM31 and the general population32–34, an increasing number of early cases of T1DM are being identified (clinical case scenario 2 in Box 1). Indeed, in the children positive for multiple islet autoantibodies detected in the FR1Da study of general population screening in Bavaria, Germany, oral glucose tolerance testing revealed that 82% of individuals were in stage 1 and 7% were in stage 2, but, remarkably, 11% were in asymptomatic stage 3 T1DM35. Similar rates (11.2%) of individuals in stage 3 were found in screening for the Diabetes Prevention Trial (DPT-1)36. However, rates were lower in antibody-positive individuals identified in other studies involving relatives of people with T1DM: 5.4% were in stage 3 in the TrialNet Pathway to Prevention study37 and 5.2% were in stage 3 at entry to the ENDIT study38. This method of presentation with T1DM is therefore likely to increase substantially if immunotherapies for T1DM prevention are licensed (which requires screening) and/or national screening programmes are introduced.

Early detection of T1DM has multiple benefits, including avoidance of acute illness or life-threatening diabetic ketoacidosis (DKA) as well as reducing hospital admissions and allowing time for structured introduction of insulin32. The indications and balance of benefits and risks of screening for T1DM have been reviewed elsewhere and pathways for clinical management of individuals found to have stage 1 or stage 2 T1DM are in development5,32. This Perspective focuses on the management of individuals found to have stage 3 T1DM, but who do not seem to immediately require insulin. To clarify this difference in clinical status, we propose that stage 3 T1DM is divided into three substages, in which stage 3a represents early disease with considerable β-cell reserve (as represented by high C-peptide levels (as a proxy for insulin levels)16) in individuals who do not require insulin (Table 1). Of note, the C-peptide thresholds referred to in Table 1 represent guide values only. Levels might need to be modified in those who are more or less insulin resistant and individualized under other circumstances (such as in individuals with a deficiency or excess of hormones that affect carbohydrate metabolism, or in people who are pregnant). The evidence supporting this subclassification is currently incomplete and more studies are required; this evidence is reviewed in the section ‘When is it safe to not use insulin in T1DM?’.

Delaying the introduction of insulin in patients with stage 3a T1DM could have many advantages. For instance, in the absence of exogenous insulin, the risk of hypoglycaemia is negligible. Once insulin is introduced, hypoglycaemia does occur even in this stage of the disease, albeit less frequently than in more advanced stages39. This finding is in part because even when residual β-cell mass is sufficient to keep T1DM asymptomatic, α-cell function is already impaired, which leads to dysregulated glucagon secretion and more marked propensity for hypoglycaemia in response to exogenous

insulin40. In addition, without insulin therapy, patients do not require carbohydrate counting or intensive monitoring of blood levels of glucose. Furthermore, lifestyle restrictions, such as monitoring of glucose levels during exercise or missed meals, are not required.

However, withholding insulin inappropriately might risk lifethreatening DKA, especially during periods of intercurrent illness. The exact criteria for starting insulin in children diagnosed in screening studies are not generally reported, and it is not clear if delaying insulin introduction after confirming stage 3 T1DM was considered in these screening studies41–43. Here, we discuss how to identify and monitor 'non-insulin-requiring T1DM', the timing of insulin introduction and possible interventions that might delay the need for insulin.

When is it safe to not use insulin in T1DM?

People affected by β-cell autoimmunity produce endogenous insulin for long periods, even during the natural course of T1DM development, and do not necessarily require exogenous insulin in stages 1 and 2 and early stage 3. The length of time spent in these early phases might be further extended by treatment with immunomodulation in the future5,44 (see the section 'Interventions that might delay the need for insulin'). Therefore, understanding and exploring how best to manage an attenuated progression through the natural history of pre-symptomatic T1DM, and possibly also stage 3a, will become increasingly important. In these stages, the need for insulin replacement should be guided by the level of endogenous insulin production and action rather than the presence of autoimmunity per se. This approach leads us to an important decision: when is it necessary to start insulin replacement, or viewed another way, when is it safe and acceptable to withhold insulin?

Table 1 | Proposed subclassification of stage 3 T1DM

Stage	Insulin requirement	Clinical features
Stage 3a	Early T1DM not requiring insulin	Not insulin-requiring; random C-peptide >600 pmol/l; HbA_{1c} 6.4–7.0% (47–53 mmol/mol) without insulin; very low ketosis risk; no hypoglycaemic risk; immunotherapy and/or β-cell-preserving therapy appropriate
Stage 3b	Requiring insulin, but clinically relevant β-cell function remains	Insulin-requiring; random C-peptide 200–600 pmol/l; immunotherapy and/or β-cell-preserving therapy appropriate; moderate ketosis and hypoglycaemia risk
Stage 3c	Requiring insulin and no clinically significant β-cell function	Random C-peptide <200 pmol/l; advanced insulin therapy and/or β-cell replacement required; high ketosis and hypoglycaemia risk

T1DM, type 1 diabetes mellitus.

Driven by fear of rapid progression to insulin deficiency and DKA, some clinicians traditionally have a low threshold for starting insulin when T1DM is suspected or confirmed, irrespective of the state of β-cell function45. In many areas of the world, the increasing availability of C-peptide testing for the assessment of endogenous insulin secretion puts clinicians in a better position to decide when insulin replacement is really required. In addition, considerable endogenous insulin production might permit a trial of non-insulin treatments to achieve desirable glycaemic control in the early stages of T1DM (see the section 'Interventions that might delay the need for insulin')

Value of measuring of C-peptide levels

In the T1DM research setting, the gold standard for the assessment of β-cell function is the mixed meal tolerance test, where the C-peptide area under the curve is measured over 120–240 min after a mixed meal challenge46. This time consuming and complex test is unsuitable for use in clinical practice and is being replaced by more practical one-off measurements of C-peptide in the serum. Measurements of serum levels of C-peptide under non-fasting conditions (taken within 1–5 h following a meal) seem to be a convenient and informative way of monitoring β-cell function in the clinical setting15. Currently available only in the research setting, C-peptide measurement from a capillary dry blood spot sample is an attractive approach as it offers the potential for frequent sampling and can be done at home47.

Measurement of C-peptide levels provides valuable information to determine the optimal time to start insulin treatment in autoimmunedriven diabetes mellitus. It is recognized that non-fasting serum levels of C-peptide below 200 pmol/l in the absence of hypoglycaemia is indicative of clinically significant insulin deficiency that might require immediate insulin replacement to prevent ketosis developing48,49. By contrast, levels greater than 600 pmol/l suggest sufficient endogenous insulin production and open up the possibility of delaying the introduction of insulin replacement and exploring non-insulin treatments15,16. This approach is discussed in more detail later in the article. Similar, although slightly higher, thresholds for starting insulin (C-peptide

The risk of long-term complications should also be considered when deciding on whether or not to start insulin therapy. However, we are not advocating avoidance of insulin in those with suboptimal glycaemic control (HbA1c >53 mmol/mol (>7%)), and hence it is unlikely that withholding insulin in individuals with stage 3a disease will adversely affect the risk of microvascular complications51.

C-peptide levels alone are insufficient to guide the timing of the introduction of insulin therapy and should be interpreted in the context of glycaemic control and clinical symptoms. In addition, frequently repeated C-peptide measurements are required in this phase as a transient increase in C-peptide levels is often seen after diagnosis of T1DM52 and can mislead clinicians to omit insulin in individuals in this stage of disease if the increase is shown by an isolated one-off measurement. In addition, it is well recognized that an accelerated decline in stimulated C-peptide levels happens ∼6 months prior to symptomatic T1DM, with a faster decline 3 months prior to the symptoms53. Implementation of careful and frequent monitoring of β-cell function would enable detection of the decline in this period and alert the individual and clinician to the imminent need for the start of insulin therapy.

Age is also an important factor to take into account, as C-peptide levels decline more rapidly in younger children (below 12 years of age) than older children and adults54. The presence of IA-2 antibodies has been identified as a factor associated with more rapid disease progression in individuals with stage 1 T1DM than in individuals with other β-cell autoantibodies, and risk scores have been calculated; however, similar scores have not been developed for progression in individuals with stage 3 T1DM55. Hence, children under the age of 12 years and those who are IA-2 antibody-positive should be monitored more frequently than older children, adults and people with other β-cell autoantibodies.

Box 2

Possible criteria for the timing of introducing insulin in stage 3a type 1 diabetes mellitus

C-peptide level
- Non-fasting <600 pmol/l

Glycaemic control
- HbA_{1c} >53 mmol/mol (7%)
- Frequent home postprandial blood levels of glucose >8 mmol/l
- Time above 8 mmol/l on a continuous glucose monitor is >10%

Diabetic ketoacidosis risk
- Episode of ketosis or ketoacidosis
- Persistent home blood levels of ketones of >0.6 mmol/l

Clinical symptoms
- Weight loss
- Reduced exercise performance
- Intercurrent illness, pregnancy, nausea or vomiting

Assessing DKA risk in those not using insulin

Population-based data published in 2021 suggest that the risk of DKA sharply reduces in individuals with a recent diagnosis of T1DM (390 pmol/l) than people with T1DM who present with DKA61. These findings suggest that with the same circulating levels of insulin, people who are insulin-sensitive achieve better glycaemic control and have lower ketosis risk than those with a greater degree of insulin resistance. Hence, C-peptide levels should be interpreted in the context of factors that affect an individual's insulin sensitivity62. There is a need for the development of a more advanced measure of β-cell function that will incorporate not only C-peptide and insulin level, but also the pattern of insulin secretion (loss of first phase insulin response)40 and the influence of glycaemic levels. A future prospective study is required to establish the right marker and its relationship to risk of severe hyperglycaemia, and especially to ketosis.

Importance of patient education and glycaemic monitoring

It is crucial to remember that T1DM is a progressive disease that can rapidly advance towards considerable insulin deficiency. The importance of education, careful monitoring and clear guidance on when to start insulin based on the glycaemic profile and C-peptide levels should be offered to all patients with known or suspected T1DM16 in whom insulin treatment is delayed. Stage 3a can potentially last several years in some patients and it is important to keep patients safe during this period. At the same time, introducing rigorous, overwhelming and perhaps counterproductive frequent testing in the name of safety can increase patient anxiety, which is important to avoid.

Easy access to diabetes mellitus teams during this period is important. Pre-symptomatic T1DM, and especially stage 3a disease, in young children (less than 12 years of age) should be managed with extra caution given the rapid progression from seroconversion to clinical T1DM in this group63. At the other end of the spectrum are patients with LADA, who progress slowly. In this group, evidence

of persistently high C-peptide levels alongside good glycaemic control would provide reassurance for the safety of withholding insulin50. Hence, β-cell function monitoring, clinical and glycaemic control criteria (Box 2) and more frequent ketone monitoring during intercurrent illness (see the last paragraph in this section) should be taken into consideration in determining the timing of starting insulin therapy in patients with LADA and young children with pre-symptomatic T1DM.

Box 2 summarizes potential criteria across different domains that might be used to guide the timing of the introduction of insulin therapy, and Fig. 1 proposes a possible approach to monitoring and management. An evidence base behind these criteria is currently lacking and should be a focus of future studies. Testing C-peptide and HbA1c levels every 3 months, combined with weekly testing of blood levels of glucose and ketones and mandatory testing during intercurrent illness64 and/or if symptoms develop seems appropriate5,32. The timing of insulin initiation might be based on a combination of biochemical and clinical criteria (Box 2). C-peptide levels consistently below 600 pmol/l or HbA1c levels above 53 mmol/mol (>7%), which would expose the patient to microvascular risk, can be justified as thresholds for starting insulin therapy; however, a lower threshold of 48 mmol/mol (6.5%) might be used to minimize cardiovascular risk19,65.

Criteria for intervention based on continuous glucose monitoring (CGM) profiles have yet to be defined but they are likely to be based on ‘time above range’ as there is not expected to be any ‘time below range’ in patients with stage 3a T1DM. In 2022, more than 10% of time above 7.8 mmol/l (140 mg/dl) was reported as a strong predictor of disease progression in people with stage 1 or stage 2 T1DM, and could be considered as a criterion for intervention66. However, it is not clear whether CGM will provide more information than weekly postprandial capillary measurements, which would be substantially less expensive. An episode of ketosis (ketones >0.6 mmol/l), and particularly ketoacidosis (pH 3.0 mmol/l, suggesting the presence of DKA or intercurrent illness, the patient should attend the emergency department68–72. Clinical symptoms (such as feeling generally unwell with osmotic symptoms, nausea, vomiting and abdominal pain) would not normally be expected if these criteria are applied, except in the context of intercurrent illness; however, the lack of the anabolic action of insulin might result in weight loss or reduced exercise performance73 (Box 2). Pregnancy would be an absolute indication for insulin initiation and close monitoring.

Interventions that might delay the need for insulin

Circulating blood levels of glucose are governed by both insulin secretion and insulin sensitivity. As insulin sensitivity decreases (moving from point 1 to point 2 in Fig. 2), insulin secretion would ideally rise to maintain euglycaemia. Where this rise in secretion does not happen, perhaps where there has been β-cell loss or dysfunction, the individual will ‘fall off’ the curve and progress to metabolic decompensation (point 2 to point 3 to point 4 in Fig. 2).

The need for exogenous insulin can therefore be delayed by therapies that increase insulin sensitivity and/or increase insulin secretion. These principles have been demonstrated clearly in pre-T2DM74. These principles are also supported in the context of T1DM, where reduced insulin sensitivity has been demonstrated to be an independent risk factor for progression to T1DM in those at risk62.

Useful information on therapies that increase insulin sensitivity and insulin secretion in pre-T1DM can be obtained from studies in people with established and newly diagnosed T1DM, respectively. These studies have the potential to inform approaches to delaying insulin treatment in the early stages of T1DM.

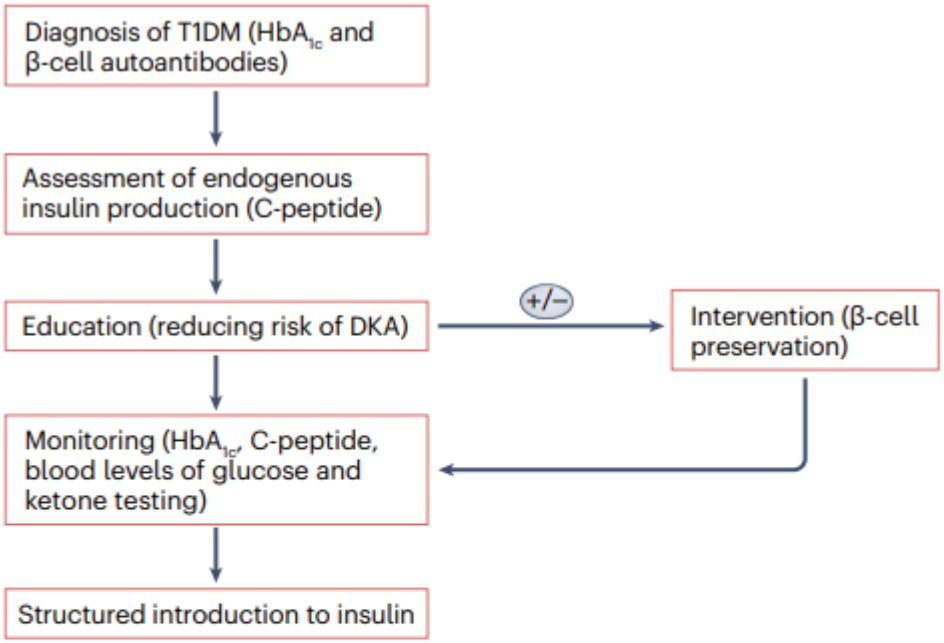

Fig. 1 | Management of stage 3a T1DM. Proposed guidance for the management of individuals diagnosed with type 1 diabetes mellitus (T1DM) and in stage 3a. The diagnosis of an autoimmune aetiology should be confirmed by islet autoantibody testing followed by assessment of β-cell function. Education refers to making all patients and their family and/or carers aware that T1DM is a progressive disease and insulin will be required at some stage, as well as making them aware of warning signs (for example, weight loss, blood levels of glucose frequently >10 mmol/l and symptoms of ketosis) and the need for periodic monitoring. For details of monitoring frequency and possible interventions, see the main text. DKA, diabetic ketoacidosis.

Agents that increase insulin sensitivity Lifestyle.

Exercise reduces insulin need75 and increases the duration of partial remission immediately after a diagnosis of T1DM. In a retrospective controlled study of individuals within 3 months of a diagnosis of T1DM (n = 48), the mean duration of partial remission (HbA1c

The feasibility of an exercise programme in patients with newonset T1DM has been trialled and no detrimental increases in glucose fluctuations (that is, DKA or severe hypoglycaemia) were demonstrated, suggesting that this exercise programme can be safely implemented in this population75,77. This was a study in adults with T1DM diagnosed within the past 3 months in which 58 participants were randomized to either usual care or to usual care plus support to exercise with the aim of exploring if the physical activity in patients with new-onset T1DM will result in an increase in insulin secretion. As such, this study is outlined in greater detail in the next section ('Agents that increase insulin secretion'). If proven to delay the need for insulin in people with pre-T1DM, exercise would form an attractive therapeutic option because of the considerable other physical and mental health benefits of exercise in T1DM78.

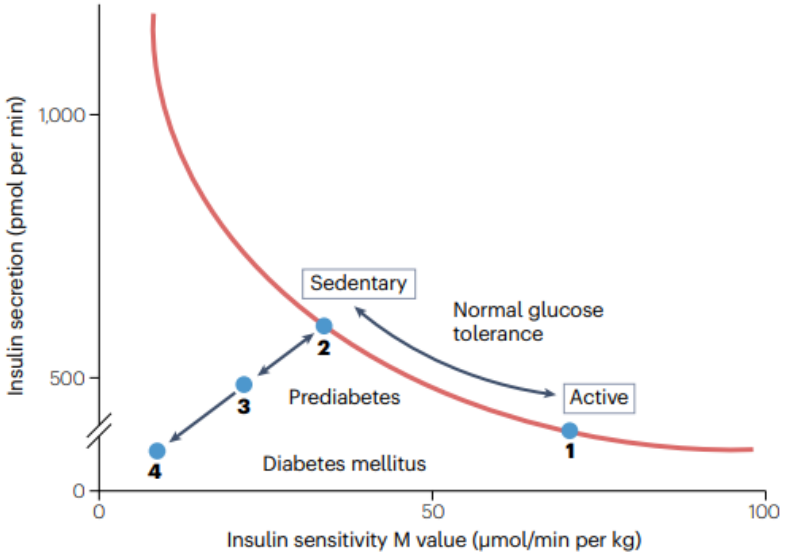

Fig. 2 | Relationship between insulin secretion and insulin sensitivity. A rise in insulin sensitivity (move from point 2 to point 1) allows a similar shift in glucose tolerance to be achieved with less insulin secretion. Conversely, a decrease in insulin sensitivity (move from point 1 to 2), as might, for example, follow a long period of reduced physical activity or weight gain, will require a greater level of insulin secretion to achieve the same shift in glucose. Insulin sensitivity and secretion are strongly linked in this reciprocal relationship. Diabetes mellitus results when this relationship cannot be maintained. Autoimmune β-cell loss limits the ramping up of insulin secretion at times of reduced insulin sensitivity, which results in a rise in blood levels of glucose and a diagnosis of type 1 diabetes mellitus. Glucose control can be maintained in the face of limited β-cell function and insulin secretion if insulin sensitivity can be increased to an extent where the residual insulin secretion is sufficient to maintain glucose control. Reprinted with permission from ref. [120], American Physiological Society.

Low carbohydrate diets reduce weight in people with T1DM79,80. Modest effects on glucose variability and no effect on HbA1c were reported, but these approaches have not been trialled in people with T1DM who retain considerable endogenous insulin secretion. However, such diets are associated with dyslipidaemia81, and dyslipidaemia in turn has recognized adverse effects on β-cells82. This potential harm makes it difficult to currently recommend low carbohydrate diets as an approach to delay the need for insulin in early stage T1DM in the absence of further studies in the population with stage 3a disease. Furthermore, any effort to incorporate low carbohydrate diets into the management of any form of diabetes mellitus must include a careful assessment of risk of disordered eating. While eating disorders do not seem to be any more prevalent in people with T1DM than in the general population, there is clear evidence that disordered eating is associated with a poorer prognosis in people with T1DM83.

Pharmacological therapies.

Metformin improves insulin sensitivity in people with T1DM84. Metformin also reduces insulin dose requirements in those with established T1DM and with overweight85, but there are no data yet as to whether metformin delays the need for insulin in people with early stage T1DM. GLP1 agonists (liraglutide) and the SGLT2 inhibitors dapagliflozin, empagliflozin and sotagliflozin all statistically significantly reduce weight and insulin dose in people with established T1DM, but we do not yet know if this will delay the need for insulin in early stage T1DM86. Liraglutide seems to have a modest effect in maintaining C-peptide levels in people with recent onset T1DM (within 20 weeks of diagnosis), although it is not clear whether this effect is due to β-cell preservation or

hyperstimulation87. A small open-label study of the SGLT2 inhibitor empagliflozin in people within 100 days of a diagnosis of T1DM demonstrated safety and acceptability and also that some participants were able to pause their meal-time insulin for over a month88. This study was not a randomized controlled study, and the absence of a non-treatment arm makes it difficult to draw conclusions, but it does demonstrate a potential for delaying insulin therapy and the potential of non-insulin therapies as an alternative to maintain glycaemic control.

There is extensive literature on the use of SGLT2 inhibitors in established T1DM, which consistently demonstrates a reduction in insulin dose, glucose variability, HbA1c and body weight without any increase in hypoglycaemia, as well as improvement in treatment satisfaction72,89–97. SGLT2 inhibitors reduce blood levels of glucose without an increase in insulin action98,99 and the resultant lower insulin dose increases the risk of ketosis and ketoacidosis100. Careful ketone monitoring is recommended68–71. However, it is anticipated that in people with stage 3a T1DM with notable β-cell reserve and a low intrinsic risk of ketosis, this risk might be less of a concern. At present there is no trial evidence that addresses this question, although in one small study, high C-peptide levels were associated with an improved reduction in HbA1c with adjuvant SGLT2 inhibitor therapy in patients with T1DM101.

Agents that increase insulin secretion Lifestyle.

Mouse and human studies demonstrate that physical activity increases insulin secretion75. The underlying mechanisms have been reviewed and relate to reduced β-cell apoptosis, increased β-cell proliferation and insulin secretion102. Direct assessment of β-cell mass and proliferation is not possible in humans. However, studies in rats have demonstrated that a 6-week programme of exercise for an hour a day for 5 days a week results in increased β-cell proliferation103,104.

Separately, different groups have demonstrated that a similar programme of exercise in rats and humans in a before and after study results in β-cells that are less prone to apoptosis when incubated with pro-inflammatory cytokines105.

Furthermore, there is now strong evidence, again from animal studies, that physical activity increases the ability of the β-cell to sense and respond to glucose. Glucose sensing by the β-cell is facilitated by cell surface glucose transporters and intracellular glucokinase, and both these proteins were increased following a programme of exercise in an ovariectomized rat model of T2DM106. The insulin content of β-cells also increased following a 6-week programme of exercise in a mouse model of T1DM107. Studies in people with or at risk of T2DM demonstrated that these findings also apply to humans102. Most exercise regimens seem to show benefit in insulin secretion but there is most evidence for moderate intensity exercise (VO2 max 40–55%) of about 200 min per week. Both aerobic and resistance exercises seem to show benefit, perhaps with greater benefit when they are combined108. In results published in 2022, serum obtained from people who had undertaken 4–12 weeks of exercise statistically significantly reduced stress-induced apoptosis of a β-cell line109. Serum from participants with T1DM or T2DM who had undertaken exercise was similarly protective. The efficiency of cytoprotection was also similar regardless of age, ethnicity, BMI or whether the participants had T1DM or T2DM, and the benefits lasted 2 months.

Based on this understanding, we have undertaken a pilot study of exercise in people with newly diagnosed T1DM (stage 3b) to explore if these benefits also translate to T1DM75. There were 58 participants diagnosed within the previous 3 months who were largely white European male individuals aged 16–60 years with a BMI of ~25 kg/m2 and an HbA1c of 75 mmol/mol (9%). They were randomized to receive either usual care or usual care plus support to exercise. This support

consisted of regular contact and encouragement to exercise but without direct supervision to do so. Physical activity was measured through questionnaires as well as with direct actigraphy at baseline and at the end of the 12-month study. Mean level of objectively measured activity increased in the intervention group and over half of the participants reached the target of ≥150 min per week of self-reported exercise on at least 42 weeks of the year. Physical activity levels fell slightly in the control group. The intervention group seemed to become more insulin-sensitive and to require less insulin, and β-cell function measured as meal-stimulated C-peptide that was corrected for the change in insulin sensitivity seemed to improve. Combined with the insulin-sensitizing effect of exercise, and the other documented benefits of exercise in T1DM on cardiovascular risk and well-being, this is a therapy worth exploring further in pre-T1DM. Low calorie diets do increase β-cell function in the context of T2DM110, but it is not clear whether this finding also applies to T1DM.

Pharmacological therapies. Therapies for β-cell preservation have been tested in people with newly diagnosed T1DM for over four decades111 and can be classed as immune-based or non-immune-based, with the former showing the most promise. A summary of the different disease target mechanisms is provided in Fig. 3. These therapies have the potential to inform approaches to preserving β-cell function and insulin secretion in early stage T1DM (stages 1–3). Several reviews of clinic trials of immunomodulatory agents for preservation of β-cell function in people with newly diagnosed T1DM have been undertaken5,111. Published in 2020, a cross-trial efficacy comparison assessed the most effective agents for β-cell preservation trialled in the past 10 years112. Analysis of covariance modelling of the different outcome measures showed that two different agents, low dose anti-thymocyte globulin (believed to work through depletion of effector T cells with relative sparing of regulatory T cells) and teplizumab (a humanized anti-CD3 monoclonal antibody targeting T cells), demonstrated most efficacy (Fig. 3). However, this review did not include trials of older agents that had previously demonstrated promise, restricted the analysis to selected studies of the chosen agents and did not explore important secondary outcomes, such as insulin dose and glucose control. Both these reviews111,112 of trials for β-cell preservation in new-onset T1DM support testing of T cell-based therapy in people before they develop T1DM. Indeed, in a trial of teplizumab administered as a daily infusion over 2 weeks to people with stage 2 T1DM, this treatment delayed the need for insulin by almost 3 years44,113.

Several other therapies tested in the new onset setting that hold promise in the prevention area are also worth highlighting (Fig. 3). Abatacept (CTLA4-Ig), an established therapeutic targeting T cell costimulation, has shown benefit in one well-controlled study114. In a trial published in 2021, the combination of liraglutide and anti-IL-21 preserved β-cell function with very few adverse outcomes87. Benefit was not demonstrated with either of these agents alone and it remains unclear how long the benefits in terms of C-peptide levels persisted.

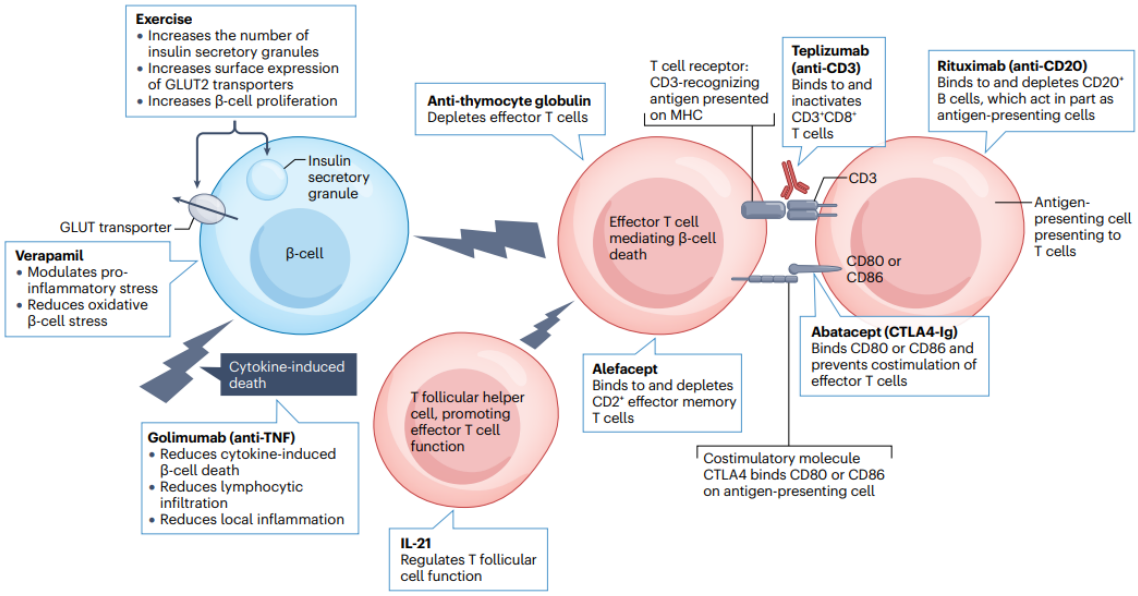

Fig. 3 | Sites of action of therapeutic interventions for β-cell preservation. All immunotherapeutic interventions outlined have published phase II efficacy data. β-Cell death is mediated through lymphocyte-mediated mechanisms. T cells are an important component of this reaction and recognize peptide fragments of β-cell proteins when they are presented by antigen-presenting anti-thymocyte globulin), the antigen-presenting cells (rituximab) or the antigen-presenting cell–T cell interaction (abatacept) have all been demonstrated to preserve β-cell function in people with newly diagnosed type 1 diabetes mellitus. β-Cell function is also preserved by agents that promote β-cell viability (verapamil, golimumab and exercise) and proliferation

In repurposing studies, verapamil (a calcium channel blocker) seems to preserve β-cell function in people with new-onset T1DM115, possibly through a reduction in levels of chromogranin A. However, it seems that ongoing treatment with verapamil is required for long-term benefit116. In a study published in 2020, subcutaneous administration of the anti-TNF monoclonal antibody, golimumab, every 2 weeks showed efficacy in preventing declines in levels of C-peptide in new-onset T1DM117. It would be appropriate to determine the potential of any or all of these treatments that slow the loss of C-peptide in people with standard new-onset T1DM (stage 3b) while still in stage 3a, when they might be expected to be able to extend the period of insulin independence. Combinations of treatments might also be considered112. Studies to define stopping criteria for these immunotherapies need to be established. As there are clear clinical benefits of even low levels of β-cell function in people with newly diagnosed T1DM who require insulin therapy77, continuing **immunotherapies might be useful even once insulin has been initiated.**

Conclusion

The advent of islet autoantibody screening for early T1DM has allowed the identification of a period between the diagnosis of T1DM by glycaemic criteria and the development of the clinical need for insulin therapy, which we propose is referred to as stage 3a T1DM. To date, this period of non-insulin-dependent T1DM has been largely unrecognized and has received very little attention from the clinical and research community. However, as autoantibody testing becomes more widespread, diagnosis of T1DM at this stage, rather than at a later stage that requires immediate insulin initiation, is likely to become more commonplace and perhaps ultimately the norm.

While an exploration of how insulin is initiated in the early stages of T1DM is beyond the scope of this Perspective, there is now compelling evidence that bolus mealtime insulin alone might be an effective initial approach to replacing the early postprandial insulin requirements that the residual β-cells present at the time of a T1DM diagnosis cannot satisfy118. In addition, there is also now strong

evidence that closed loop insulin delivery is effective at achieving and maintaining effective glucose control from diagnosis119.

Currently, the number of patients identified with stage 3a disease is small, but intervention in the disease process at this stage might delay the need for insulin by months or years, avoiding the need for lifestyle restrictions, glucose monitoring and insulin administration. The suggestions we have made in this article need to be tested in formal and adequately powered clinical trials, but it is clear there is an emerging need for clinical studies in stage 3a T1DM to guide the safe management of children and adults without insulin and to define ways to lengthen this period for as long as is safely possible.

References

1. Greenbaum, C. J. et al. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. Diabetes 61, 2066–2073 (2012).

2. Oram, R. A., Sims, E. K. & Evans-Molina, C. Beta cells in type 1 diabetes: mass and function; sleeping or dead? Diabetologia 62, 567–577 (2019).

3. Powers, A. C. Type 1 diabetes mellitus: much progress, many opportunities. J. Clin. Invest. 131, e142242 (2021).

4. Carr, A. L. J. et al. Circulating C-peptide levels in living children and young people and pancreatic β-cell loss in pancreas donors across type 1 diabetes disease duration. Diabetes 71, 1591–1596 (2022).

5. Tatovic, D. & Dayan, C. M. Replacing insulin with immunotherapy: time for a paradigm change in type 1 diabetes. Diabet. Med. 38, e14696 (2021).

6. Mathieu, C., Martens, P. J. & Vangoitsenhoven, R. One hundred years of insulin therapy. Nat. Rev. Endocrinol. 17, 715–725 (2021).

7. Russell-Jones, D. & Herring, R. 100 years of physiology, discrimination and wonder. Diabet. Med. 38, e14642 (2021).

8. Sims, E. K., Carr, A. L. J., Oram, R. A., DiMeglio, L. A. & Evans-Molina, C. 100 years of insulin: celebrating the past, present and future of diabetes therapy. Nat. Med. 27, 1154–1164 (2021).

9. Miller, K. M. et al. Current state of type 1 diabetes treatment in the US: updated data from the T1D Exchange clinic registry. Diabetes Care 38, 971–978 (2015).

10. McKnight, J. A. et al. Glycaemic control of type 1 diabetes in clinical practice early in the 21st century: an international comparison. Diabet. Med. 32, 1036–1050 (2015).

11. Wasag, D. R., Gregory, J. W., Dayan, C., Harvey, J. N. & Brecon, G. Excess all-cause mortality before age 30 in childhood onset type 1 diabetes: data from the Brecon Group Cohort in Wales. Arch. Dis. Child. 103, 44–48 (2018).

12. Foster, N. C. et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016–2018. Diabetes Technol. Ther. 21, 66–72 (2019).

13. Anderzen, J. et al. International benchmarking in type 1 diabetes: large diference in childhood HbA1c between eight high-income countries but similar rise during adolescence – a quality registry study. Pediatr. Diabetes 21, 621–627 (2020).

14. Prigge, R. et al. International comparison of glycaemic control in people with type 1 diabetes: an update and extension. Diabet. Med. 39, e14766 (2022).

15. Jones, A. G. & Hattersley, A. T. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet. Med. 30, 803–817 (2013).

16. Tatovic, D. et al. Diagnosing type 1 diabetes in adults: guidance from the UK T1D immunotherapy consortium. Diabet. Med. 39, e14862 (2022).

17. Food and Drug Administration. FDA approves first drug that can delay onset of type 1 diabetes. FDA https://www.fda.gov/news-events/press-announcements/fda-approvesfirst-drug-can-delay-onset-type-1-diabetes (2022).

18. Couper, J. J. et al. ISPAD clinical practice consensus guidelines 2018: stages of type 1 diabetes in children and adolescents. Pediatr. Diabetes 19, 20–27 (2018).

19. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes — 2021. Diabetes Care 44, S15–S33 (2021).

20. Ziegler, A. G. et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 309, 2473–2479 (2013).

21. Insel, R. A. et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care 38, 1964–1974 (2015).

22. Cherubini, V. et al. Temporal trends in diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes between 2006 and 2016: results from 13 countries in three continents. Diabetologia 63, 1530–1541 (2020).

23. Ng, S. M. et al. Presentation of newly diagnosed type 1 diabetes in children and young people during COVID-19: a national UK survey. BMJ Paediatr. Open 4, e000884 (2020).

24. Karges, B. et al. A comparison of familial and sporadic type 1 diabetes among young patients. Diabetes Care 44, 1116–1124 (2021).

25. Atkinson, M. A., Campbell-Thompson, M., Kusmartseva, I. & Kaestner, K. H. Organisation of the human pancreas in health and in diabetes. Diabetologia 63, 1966–1973 (2020).

26. Bingley, P. J. & Williams, A. J. Islet autoantibody testing: an end to the trials and tribulations? Diabetes 62, 4009–4011 (2013).

27. Wyatt, R. & Williams, A. J. Islet autoantibody analysis: radioimmunoassays. Methods Mol. Biol. 1433, 57–83 (2016).

28. Lampasona, V. & Liberati, D. Islet autoantibodies. Curr. Diab Rep. 16, 53 (2016).

29. Williams, C. L. & Long, A. E. What has zinc transporter 8 autoimmunity taught us about type 1 diabetes? Diabetologia 62, 1969–1976 (2019).

30. So, M. et al. Advances in type 1 diabetes prediction using islet autoantibodies: beyond a simple count. Endocr. Rev. 42, 584–604 (2021).

31. Besser, R. E. J., Ng, S. M. & Robertson, E. J. Screening children for type 1 diabetes. BMJ 375, e067937 (2021).

32. Besser, R. E. J. et al. General population screening for childhood type 1 diabetes: is it time for a UK strategy? Arch. Dis. Child. 107, 790–795 (2022).

33. Sims, E. K. et al. Screening for type 1 diabetes in the general population: a status report and perspective. Diabetes 71, 610–623 (2022).

34. Quinn, L. M. et al. EarLy surveillance for autoimmune diabetes: protocol for a qualitative study of general population and stakeholder perspectives on screening for type 1 diabetes in the UK (ELSA 1). BMJ Open Diabetes Res. Care 10, e002750 (2022).

35. Ziegler, A. G. et al. Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. JAMA 323, 339–351 (2020).

36. Diabetes Prevention Trial – Type 1 Diabetes Study Group. Efects of insulin in relatives of patients with type 1 diabetes mellitus. N. Engl. J. Med. 346, 1685–1691 (2002).

37. Mahon, J. L. et al. The TrialNet natural history study of the development of type 1 diabetes: objectives, design, and initial results. Pediatr. Diabetes 10, 97–104 (2009).

38. Gale, E. A., Bingley, P. J., Emmett, C. L. & Collier, T. European Nicotinamide Diabetes Intervention Trial (ENDIT) Group.European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. Lancet 363, 925–931 (2004).

39. Malkani, S. & Kotwal, A. Frequency and predictors of self-reported hypoglycemia in insulin-treated diabetes. J. Diabetes Res. 2017, 7425925 (2017).

40. Flatt, A. J. S., Greenbaum, C. J., Shaw, J. A. M. & Rickels, M. R. Pancreatic islet reserve in type 1 diabetes. Ann. NY Acad. Sci. 1495, 40–54 (2021).

41. Barker, J. M. et al. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. Diabetes Care 27, 1399–1404 (2004).

42. Steck, A. K. et al. Predictors of progression from the appearance of islet autoantibodies to early childhood diabetes: the environmental determinants of diabetes in the young (TEDDY). Diabetes Care 38, 808–813 (2015).

43. Steck, A. K. et al. Residual beta-cell function in diabetes children followed and diagnosed in the TEDDY study compared to community controls. Pediatr. Diabetes 18, 794–802 (2017).

44. Herold, K. C. et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N. Engl. J. Med. 381, 603–613 (2019).

45. Foteinopoulou, E. et al. Impact of routine clinic measurement of serum C-peptide in people with a clinician-diagnosis of type 1 diabetes. Diabet. Med. 38, e14449 (2021).

46. Greenbaum, C. J. et al. Mixed-meal tolerance test versus glucagon stimulation test for the assessment of β-cell function in therapeutic trials in type 1 diabetes. Diabetes Care 31, 1966–1971 (2008).

47. Willemsen, R. H. et al. Frequent monitoring of C-peptide levels in newly diagnosed type 1 subjects using dried blood spots collected at home. J. Clin. Endocrinol. Metab. 103, 3350–3358 (2018).

48. Marren, S. M. et al. Persistent C-peptide is associated with reduced hypoglycaemia but not HbA1c in adults with longstanding type 1 diabetes: evidence for lack of intensive treatment in UK clinical practice? Diabet. Med. 36, 1092–1099 (2019).

49. Taylor, G. S. et al. Capturing the real-world benefit of residual β-cell function during clinically important time-periods in established type 1 diabetes. Diabet. Med. 39, e14814 (2022).

50. Buzzetti, R. et al. Management of latent autoimmune diabetes in adults: a consensus statement from an international expert panel. Diabetes 69, 2037–2047 (2020).

51. Jeyam, A. et al. Clinical impact of residual C-peptide secretion in type 1 diabetes on glycemia and microvascular complications. Diabetes Care 44, 390–398 (2021).

52. Yki-Jarvinen, H. & Koivisto, V. A. Natural course of insulin resistance in type I diabetes. N. Engl. J. Med. 315, 224–230 (1986).

53. Sosenko, J. M. et al. Glucose and C-peptide changes in the perionset period of type 1 diabetes in the diabetes prevention trial-type 1. Diabetes Care 31, 2188–2192 (2008).

54. Hao, W. et al. Fall in C-peptide during first 4 years from diagnosis of type 1 diabetes: variable relation to age, HbA1c, and insulin dose. Diabetes Care 39, 1664–1670 (2016).

55. Weiss, A. et al. Progression likelihood score identifies substages of presymptomatic type 1 diabetes in childhood public health screening. Diabetologia 65, 2121–2131 (2022).

56. Mortensen, H. B. et al. Multinational study in children and adolescents with newly diagnosed type 1 diabetes: association of age, ketoacidosis, HLA status, and autoantibodies on residual beta-cell function and glycemic control 12 months after diagnosis. Pediatr. Diabetes 11, 218–226 (2010).

57. Ludvigsson, J. et al. C-peptide in the classification of diabetes in children and adolescents. Pediatr. Diabetes 13, 45–50 (2012).

58. Lee, T. H. et al. The clinical measures associated with C-peptide decline in patients with type 1 diabetes over 15 years. J. Korean Med. Sci. 28, 1340–1344 (2013).

59. Govan, L. et al. Achieved levels of HbA1c and likelihood of hospital admission in people with type 1 diabetes in the Scottish population: a study from the Scottish Diabetes Research Network Epidemiology Group. Diabetes Care 34, 1992–1997 (2011).

60. Thunander, M. et al. Levels of C-peptide, body mass index and age, and their usefulness in classification of diabetes in relation to autoimmunity, in adults with newly diagnosed diabetes in Kronoberg, Sweden. Eur. J. Endocrinol. 166, 1021–1029 (2012).

61. Wang, Z. H., Kihl-Selstam, E. & Eriksson, J. W. Ketoacidosis occurs in both type 1 and type 2 diabetes – a population-based study from Northern Sweden. Diabet. Med. 25, 867–870 (2008).

62. Fourlanos, S., Narendran, P., Byrnes, G. B., Colman, P. G. & Harrison, L. C. Insulin resistance is a risk factor for progression to type 1 diabetes. Diabetologia 47, 1661–1667 (2004).

63. Besser, R. E. J. et al. ISPAD clinical practice consensus guidelines 2022: stages of type 1 diabetes in children and adolescents. Pediatr. Diabetes 23, 1175–1187 (2022).

64. Ooi, E. et al. Clinical and biochemical profile of 786 sequential episodes of diabetic ketoacidosis in adults with type 1 and type 2 diabetes mellitus. BMJ Open Diabetes Res. Care 9, e002451 (2021).

65. Cavero-Redondo, I., Peleteiro, B., Alvarez-Bueno, C., Rodriguez-Artalejo, F. & Martinez-Vizcaino, V. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. BMJ Open 7, e015949 (2017).

66. Steck, A. K. et al. CGM metrics predict imminent progression to type 1 diabetes: autoimmunity screening for kids (ASK) study. Diabetes Care 45, 365–371 (2022).

67. Dhatariya, K. K., Joint British Diabetes Societies for Inpatient Care. The management of diabetic ketoacidosis in adults – an updated guideline from the Joint British Diabetes Society for Inpatient Care. Diabet. Med. 39, e14788 (2022).

68. Garg, S. K., Peters, A. L., Buse, J. B. & Danne, T. Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors: a STICH protocol. Diabetes Technol. Ther. 20, 571–575 (2018).

69. Goldenberg, R. M., Gilbert, J. D., Hramiak, I. M., Woo, V. C. & Zinman, B. Sodium-glucose co-transporter inhibitors, their role in type 1 diabetes treatment and a risk mitigation strategy for preventing diabetic ketoacidosis: the STOP DKA protocol. Diabetes Obes. Metab. 21, 2192–2202 (2019).

70. Danne, T. et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. Diabetes Care 42, 1147–1154 (2019).

71. Teng, R. et al. Comparison of protocols to reduce diabetic ketoacidosis in patients with type 1 diabetes prescribed a sodium-glucose cotransporter 2 inhibitor. Diabetes Spectr. 34, 42–51 (2021).

72. Dashora, U. et al. Association of British Clinical Diabetologists (ABCD) and Diabetes UK joint position statement and recommendations on the use of sodium-glucose cotransporter inhibitors with insulin for treatment of type 1 diabetes (updated October 2020). Diabet. Med. 38, e14458 (2021).

73. Biolo, G., Declan Fleming, R. Y. & Wolfe, R. R. Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle. J. Clin. Invest. 95, 811–819 (1995).

74. Knowler, W. C. et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N. Engl. J. Med. 346, 393–403 (2002).

75. Narendran, P. et al. Exercise to preserve β-cell function in recent-onset type 1 diabetes mellitus (EXTOD) – a randomized controlled pilot trial. Diabet. Med. 34, 1521–1531 (2017).

76. Chetan, M. R. et al. The type 1 diabetes 'honeymoon' period is five times longer in men who exercise: a case-control study. Diabet. Med. 36, 127–128 (2019).

77. Carr, A. L. J. et al. Measurement of peak C-peptide at diagnosis informs glycemic control but not hypoglycemia in adults with type 1 diabetes. J. Endocr. Soc. 5, bvab127 (2021).

78. Chimen, M. et al. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. Diabetologia 55, 542–551 (2012).

79. Musil, F. et al. Efect of low calorie diet and controlled fasting on insulin sensitivity and glucose metabolism in obese patients with type 1 diabetes mellitus. Physiol. Res. 62, 267–276 (2013).

80. Schmidt, S. et al. Low versus high carbohydrate diet in type 1 diabetes: a 12-week randomized open-label crossover study. Diabetes Obes. Metab. 21, 1680–1688 (2019).

81. Seckold, R., Fisher, E., de Bock, M., King, B. R. & Smart, C. E. The ups and downs of low-carbohydrate diets in the management of type 1 diabetes: a review of clinical outcomes. Diabet. Med. 36, 326–334 (2019).

82. Ma, M. et al. Triglyceride is independently correlated with insulin resistance and islet beta cell function: a study in population with diferent glucose and lipid metabolism states. Lipids Health Dis. 19, 121 (2020).

83. Pursey, K. M., Hart, M., Jenkins, L., McEvoy, M. & Smart, C. E. Screening and identification of disordered eating in people with type 1 diabetes: a systematic review. J. Diabetes Complicat. 34, 107522 (2020).

84. Cree-Green, M. et al. Metformin improves peripheral insulin sensitivity in youth with type 1 diabetes. J. Clin. Endocrinol. Metab. 104, 3265–3278 (2019).

85. Vella, S. et al. The use of metformin in type 1 diabetes: a systematic review of eficacy. Diabetologia 53, 809–820 (2010).

86. Tandon, S., Ayis, S., Hopkins, D., Harding, S. & Stadler, M. The impact of pharmacological and lifestyle interventions on body weight in people with type 1 diabetes: a systematic review and meta-analysis. Diabetes Obes. Metab. 23, 350–362 (2021).

87. von Herrath, M. et al. Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol. 9, 212–224 (2021).

88. Wentworth, J. M., Fourlanos, S., Colman, P. G. & Harrison, L. C. A pilot study of the feasibility of empagliflozin in recent-onset type 1 diabetes. Metab. Open 5, 100021 (2020).

89. Garg, S. K. et al. Efects of sotagliflozin added to insulin in patients with type 1 diabetes. N. Engl. J. Med. 377, 2337–2348 (2017).

90. Rosenstock, J. et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. Diabetes Care 41, 2560–2569 (2018).

91. Buse, J. B. et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the North American inTandem1 Study. Diabetes Care 41, 1970–1980 (2018).

92. Perkins, B. A. et al. Exploring patient preferences for adjunct-to-insulin therapy in type 1 diabetes. Diabetes Care 42, 1716–1723 (2019).

93. Ervin, C. et al. Insights into patients' experience with type 1 diabetes: exit interviews from phase III studies of sotagliflozin. Clin. Ther. 41, 2219–2230.e6 (2019).

94. Ehrmann, D. et al. Risk factors and prevention strategies for diabetic ketoacidosis in people with established type 1 diabetes. Lancet Diabetes Endocrinol. 8, 436–446 (2020).

95. Rao, L., Ren, C., Luo, S., Huang, C. & Li, X. Sodium-glucose cotransporter 2 inhibitors as an add-on therapy to insulin for type 1 diabetes mellitus: meta-analysis of randomized controlled trials. Acta Diabetol. 58, 869–880 (2021).

96. Phillip, M. et al. Long-term eficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: pooled 52-week outcomes from the DEPICT-1 and -2 studies. Diabetes Obes. Metab. 23, 549–560 (2021).

97. Seufert, J. et al. Real-world data of 12-month adjunct sodium-glucose co-transporter-2 inhibitor treatment in type 1 diabetes from the German/Austrian DPV registry: improved HbA1c without diabetic ketoacidosis. Diabetes Obes. Metab. 24, 742–746 (2022).

98. Herring, R. A. et al. Metabolic efects of an SGLT2 inhibitor (dapagliflozin) during a period of acute insulin withdrawal and development of ketoacidosis in people with type 1 diabetes. Diabetes Care 43, 2128–2136 (2020).

99. Hampp, C. et al. Use of sodium-glucose cotransporter 2 inhibitors in patients with type 1 diabetes and rates of diabetic ketoacidosis. Diabetes Care 43, 90–97 (2020).

100. Musso, G., Sircana, A., Saba, F., Cassader, M. & Gambino, R. Assessing the risk of ketoacidosis due to sodium-glucose cotransporter (SGLT)-2 inhibitors in patients with type 1 diabetes: a meta-analysis and meta-regression. PLoS Med. 17, e1003461 (2020).

101. Shimoda, M. et al. Eficacy and safety of adding ipragliflozin to insulin in Japanese patients with type 1 diabetes mellitus: a retrospective study. Endocr. J. 68, 1455–1461 (2021).

102. Curran, M. et al. The benefits of physical exercise for the health of the pancreatic β-cell: a review of the evidence. Exp. Physiol. 105, 579–589 (2020).

103. Choi, S. B., Jang, J. S., Hong, S. M., Jun, D. W. & Park, S. Exercise and dexamethasone oppositely modulate β-cell function and survival via independent pathways in 90% pancreatectomized rats. J. Endocrinol. 190, 471–482 (2006).

104. Kiraly, M. A. et al. Attenuation of type 2 diabetes mellitus in the male Zucker diabetic fatty rat: the efects of stress and non-volitional exercise. Metabolism 56, 732–744 (2007).

105. Paula, F. M. M. et al. Exercise training protects human and rodent β cells against endoplasmic reticulum stress and apoptosis. FASEB J. 32, 1524–1536 (2018).

106. Choi, S. B., Jang, J. S. & Park, S. Estrogen and exercise may enhance β-cell function and mass via insulin receptor substrate 2 induction in ovariectomized diabetic rats. Endocrinology 146, 4786–4794 (2005).

107. Huang, H. H. et al. Exercise increases insulin content and basal secretion in pancreatic islets in type 1 diabetic mice. Exp. Diabetes Res. 2011, 481427 (2011).

108. AbouAssi, H. et al. The efects of aerobic, resistance, and combination training on insulin sensitivity and secretion in overweight adults from STRRIDE AT/RT: a randomized trial. J. Appl. Physiol. 118, 1474–1482 (2015).

109. Coomans de Brachène, A. et al. Exercise as a non-pharmacological intervention to protect pancreatic beta cells in individuals with type 1 and type 2 diabetes. Diabetologia 66, 450–460 (2022).

110. Jackness, C. et al. Very low-calorie diet mimics the early beneficial efect of Roux-en-Y gastric bypass on insulin sensitivity and β-cell function in type 2 diabetic patients. Diabetes 62, 3027–3032 (2013).

111. Allen, L. A. & Dayan, C. M. Immunotherapy for type 1 diabetes. Br. Med. Bull. 140, 76–90 (2021).

112. Jacobsen, L. M. et al. Comparing beta cell preservation across clinical trials in recent-onset type 1 diabetes. Diabetes Technol. Ther. 22, 948–953 (2020).

113. Sims, E. K. et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci. Transl Med. 13, eabc8980 (2021).

114. Orban, T. et al. Costimulation modulation with abatacept in patients with recentonset type 1 diabetes: follow-up 1 year after cessation of treatment. Diabetes Care 37, 1069–1075 (2014).

115. Ovalle, F. et al. Verapamil and beta cell function in adults with recent-onset type 1 diabetes. Nat. Med. 24, 1108–1112 (2018).

116. Xu, G. et al. Exploratory study reveals far reaching systemic and cellular efects of verapamil treatment in subjects with type 1 diabetes. Nat. Commun. 13, 1159 (2022).

117. Quattrin, T. et al. Golimumab and beta-cell function in youth with new-onset type 1 diabetes. N. Engl. J. Med. 383, 2007–2017 (2020).

118. Hopkinson, H. E., White, A. D., Nightingale, P. & Narendran, P. A novel approach to basal-bolus insulin initiation in adults with newly diagnosed type 1 diabetes: an observational cohort study of a service redesign. Br. J. Diabetes 18, 71–75 (2018).

119. Boughton, C. K. et al. Closed-loop therapy and preservation of C-peptide secretion in type 1 diabetes. N. Engl. J. Med. 387, 882–893 (2022).

120. Roberts, C. K., Hevener, A. L. & Barnard, R. J. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. Compr. Physiol. https://doi.org/10.1002/cphy.c110062 (2013).