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Lessons and gaps in the prediction and prevention of type 1 diabetes

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ABSTRACT

Type 1 diabetes (T1D) is a serious chronic autoimmune condition. Even though the root cause of T1D development has yet to be determined, enough is known about the natural history of T1D pathogenesis to allow study of interventions that may delay or even prevent the onset of hyperglycemia and clinical T1D. Primary prevention aims to prevent the onset of beta cell autoimmunity in asymptomatic people at high genetic risk for T1D. Secondary prevention strategies aim to preserve functional beta cells once autoimmunity is present, and tertiary prevention aims to initiate and extend partial remission of beta cell destruction after the clinical onset of T1D. The approval of teplizumab in the United States to delay the onset of clinical T1D marks an impressive milestone in diabetes care. This treatment opens the door to a paradigm shift in T1D care. People with T1D risk need to be identified early by measuring T1D related islet autoantibodies. Identifying people with T1D before they have symptoms will facilitate better understanding of pre-symptomatic T1D progression and T1D prevention strategies that may be effective.

1. Introduction

Type 1 diabetes (T1D) is a chronic autoimmune condition that results from complex interactions between the immune system, genes, and environment. The estimated prevalence of T1D among youth age 19 years or younger is increasing in many areas of the world, especially in young children.[1–3] T1D is a significant and costly health problem because individuals affected by T1D require life-long intensive insulin therapy and are at risk for acute metabolic complications such as diabetic ketoacidosis, long term vascular and cardiac complications, high-risk pregnancies and a reduced life expectancy.[4] Although the etiology of T1D remains incompletely understood, research has greatly clarified the natural history of T1D. Importantly, islet autoantibodies (IA) are biomarkers that can be detected in serum and allow for early identification of a person who is at high risk T1D development.[5] Predicting who will develop T1D has opened the door to investigating interventions that aim to slow the autoimmune disease process and delay or even prevent the onset of hyperglycemia and clinical T1D. [6] In this manuscript we review key knowledge related to the prediction and prevention of T1D in youth, with a focus on both pharmacological and non-pharmacological prevention.

2. Prediction of type 1 diabetes

The basic natural history of T1D is explained by the Eisenbarth model where, in the presence of genetic risk, an undetermined environmental exposure initiates autoimmune destruction of insulin-producing beta cells.[7] Serological biomarkers of islet autoimmunity are present at the time of autoimmune destruction, and children with two or more islet autoantibodies have a 70% 10-year risk and a 84% 15 year risk of developing clinical T1D from the time of seroconversion.[8] This risk declines with age, and according to autoantibody type and metabolic status.[9] To better characterize T1D risk, stages of T1D were developed in recent years with Stage 1 defined as the presence of multiple IA with normoglycemia, Stage 2 as the presence of IA with asymptomatic dysglycemia, and Stage 3 as the onset of clinical hyperglycemia and symptomatic disease (polyuria, polydipsia, weight loss, etc.) (Fig. 1).[10,11] Although staging has helped identify individuals at the highest risk for progression to clinical T1D (stage 2 T1D), determining the time from IA development to dysglycemia that results from

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destruction of a critical mass of beta-cells and beta cell dysfunction is less well characterized. The heterogeneity of T1D, described as endotypes that are defined by pathophysiological and biological features such as age, is part of what makes prediction time to progression difficult. [12–15].

2.1. Serological biomarkers in the prediction of type 1 diabetes

T1D related islet autoantibodies (IA) have long been the standard immune biomarker used to characterize the risk for development of T1D. IA against insulinoma-associated antigen-2 (IA-2), glutamic acid decarboxylase (GAD), zinc-transporter 8 (ZnT8), and insulin (IAA) are indicative of beta cell dysfunction and/or death.[16] IA rarely appear before 6 months of age, yet the peak incidence of development of the first IA is before the age of 3 years.[14,17,18] Younger age, multiple T1D related IA and presence of IA-2A have both been associated with increased risk of progression to clinical disease.[5] The level of IA may also confer risk with higher IAA and IA-2 levels associated with progression 5 years after appearance of autoantibodies in some but not all cohorts of children followed for development of T1D.[19,20] Most research has utilized radiobinding assays in research labs with high performance in the biannual Islet Autoantibody Standardization Program for T1D associated IA[21]. However, IA assays using electrochemiluminescence detection (ECL) and luciferase immunoprecipitation system (LIPS) may improve the ability to predict time to T1D in people with IA.[21–24] Other immune biomarkers including the measurement of T-cell subsets and antigen specificity are a focus of research but are currently limited clinically due to blood volume requirements being large and technical challenges using frozen and thawed blood samples. [25].

2.2. Genetic risk in the prediction of type 1 diabetes

2.2.1. High risk HLA genes confer high risk of development of type 1 diabetes and autoimmunity

The human leukocyte (*HLA*) antigen class-II region, which encodes the major histocompatibility complex (MHC), has long been known to confer risk for development of T1D.[26–28] The highest risk gene contributions are within the *HLA-DR* and *HLA-DQ* alleles.[29–33] Birth cohort studies such as DAISY, TEDDY, DIPP and BABYDIAB have been instrumental in understanding how to predict who may go on to develop T1D. The presence of *HLA-DR3* or *HLA-DR4* increases the risk for T1D development, and 95% of non-Hispanic white youth with T1D have one or both HLA haplotypes. However, using *HLA* alone to screen for T1D risk will not work. First, nearly 50% of people in the United States have *HLA-DR3* or *HLA-DR4*, yet $< 1\%$ of these people develop T1D. In the DAISY study, if a sibling of an affected proband had the same high-risk *HLA-DR3* or *HLA-DR4* haplotype as the proband, the sibling was at a much higher risk than siblings who shared none or just one high risk *HLA* haplotype.[34] Importantly, as T1D is increasing in non-European white populations, diversity in *HLA* haplotypes should be considered [35]. For example, African Americans with subsets of the DR4/DR9 genotype exhibit extremely high risk for the development of T1D [36] and more should be done to characterize HLA susceptibility in non-European populations [37].

HLA genotype is also related to the timing of islet autoimmunity development. In data from the TEDDY study (also a birth cohort study), infants with high-risk *HLA* genotypes (DR 3/4, DR 4/8, DR 4/4 and DR 3/3) were followed for the development of islet autoimmunity from birth. IA were found in 6.5% of children after follow-up over 6 years. [38] The incidence of IAA peaked in the first year of life and then declined in the following 5 years whereas GADA increased in the second year of life and remained constant. When separated by high-risk *HLA*

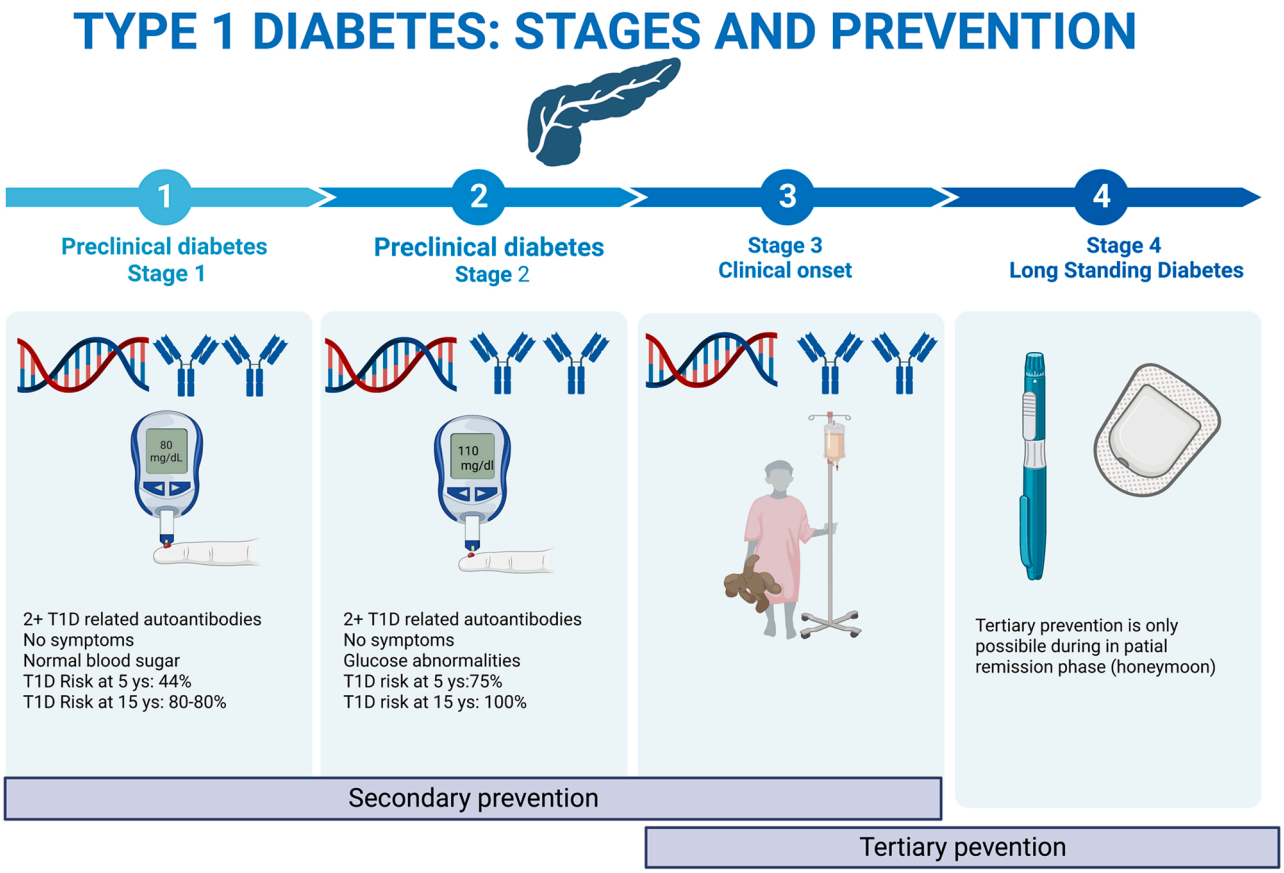

Fig. 1. Stages and prevention of type 1 diabetes.

genotype (DR 3/4, DR 4/8, DR 4/4 and DR 3/3), IA develop at different times based on genotype.[39] Development of only GADA was more common in children with the *HLA DR 3/3* genotype but less common in the children with the *HLA DR4/8* genotype, suggesting that *HLA* genotype contributes to the type and timing of IA development. Given the heterogeneity that can exist between different genotypes and IA development, this suggests that risk for development of T1D could be associated with distinct pathobiological endotypes.[12,40].

2.2.2. Non-HLA genes confer risk for type 1 diabetes

Development of T1D is highly heterogenous, as many factors can contribute to the onset and progression of islet autoimmunity. Studies have identified over 81 risk alleles for T1D, of which approximately two-thirds represent mutations associated with genes expressed in beta cells.[28,41,42] Genes in *PTPN22*, *INS*, and *NRP1, ERBB3*, *UBASH3A*, *PTPN2, IFIH1*, and *FUT2* have been associated with seroconversion to autoimmunity.[43–47] Progression from islet autoimmunity to clinical T1D have been associated with *UBASH3A*, *IFIH1*, *PTPN2, INS*, *STAT4, CD226*, and *PTPN22* among others. [43,44,46,48] SNPs within these genes are also associated with development of specific IA which once again suggest that there are distinct endotypes in T1D.[12] Similar to the *HLA DR4* haplotype,[49] risk SNPs in *PTPN22* and *STAT4* are associated with early development of IAA autoimmunity.[44] In comparison *HLA DR3* and *ERBB3* have been associated with GADA development.[44,50].

2.2.3. Genetic risk scores are models for prediction of T1D

Genetic risk scores (GRS)[51–53] utilize *HLA* and multiple non-*HLA*-risk genes to model the prediction of autoimmunity, progression to T1D, and to distinguish between type 1, type 2 and genetic forms diabetes.[54–56] Initial development of a GRS included a 40 SNP panel, called the GRS1.[52] Since initial development, further refinement of these scores to the GRS2 has been highly useful for classifying T1D, predicting progression and discriminating T1D in non-Caucasian populations. [53,57–59].

3. Progression of type 1 diabetes

3.1. Type 1 diabetes is heterogeneous in progression

Development of T1D is highly heterogenous, and genetics, diet, and viruses have all been implicated in the onset of T1D autoimmunity and progression to clinical disease. [50,60–63]. One of the biggest challenges in the understanding of T1D is knowing which individuals will, with 100% certainty, progress to clinical T1D and over what time the progression will occur. Although factors such as BMI, age and antibody titers may all contribute to the heterogeneity in timing of progression from autoimmunity to T1D, time to clinical T1D development cannot be determined at an individual level. [5,8,50,64–67] Histological analyses of pancreas from humans and mice at various stages of T1D indicate that there is a progressive increase in of markers of “stress”, insulitis, and/or abnormal function within islets, followed by transition to insulin negative pseudoatrophic islets.[68–70] The amount of residual beta cell mass at onset is also highly variable.[71].

3.1.1. Partial Remission of type 1 diabetes is a period of prolonged endogenous beta cell function

A significant proportion of subjects with T1D experience a period of partial remission (PRM) or “honeymoon” shortly after exogenous insulin therapy is begun and hyperglycemia corrected, with prevalence ranging from 40% to 80% in different populations.[72–75] The time of onset and duration of the PRM period vary significantly between individuals. This time of decreased insulin requirements due to improved endogenous beta cell function usually begins in the first 6 months post-diagnosis, with a peak incidence at 3 months.[76] The “honeymoon” then lasts anywhere from 0.5 to sometimes more than 50 months, with a median duration of ~9 months.[76,77] PRM has been defined by calculation of insulin dose adjusted HbA1c (IDAA1C- hba1c+ 4 x insulin dose), with a cut-off of ≤ 9. IDAA1C has been suggested as a surrogate for estimating beta cell function, with values ≤ 9 taken as indicative of stimulated C-peptide > 300 pmol/l.[78] Importantly, people who experience PRM have significantly fewer and/or less severe diabetic complications than those who do not.[79,80] Genetics can also influence the preservation of endogenous beta cell function soon after diagnosis.[81–84] The precise mechanisms and genetic factors responsible for the onset of the honeymoon period are still incompletely understood.[72].

3.1.2. Markers of endogenous beta cell function help quantify type 1 diabetes progression

C-peptide is a surrogate marker for endogenous insulin production and is the primary test used to determine endogenous beta cell function. Post-onset stimulated C-peptide typically declines exponentially.[85] However, while decline is predictable on a population basis, individually it is highly heterogeneous. Certain T1D SNPs have been associated with C-peptide preservation.[86–90] The gold standard test to assess beta cell function is a mixed meal tolerance test (MMTT), which measures endogenous stimulated C-peptide response to a weight based liquid meal such as Boost.[91] MMTTs are time consuming and require venipuncture to obtain serum for C-peptide measurements. Markers of beta cell reserve such as dried blood spot (DBS) C-peptide, random C-peptide and urinary C-peptide can be used to measure endogenous function and may be more feasible in a clinical setting. [85,92] Pro-insulin to C-peptide (PI:C) ratios correlate with progression to T1D and they may also be used to stratify risk progression in research and clinical settings [93,94] C-peptide preservation can improve diabetes control and decrease the risk for diabetes complications, which is why AUC C-peptide from a MMTT is most often the primary endpoint in T1D prevention research trials.[95–97].

3.2. Prevention of type 1 diabetes

While genetics, IA status, and glycemic status can be used to inform the risk of T1D development and progression, prevention of T1D has proved to be an elusive challenge. Many immunomodulatory and/or immunosuppressive agents have been investigated alone or in combinations to halt or delay progression of beta cell destruction and have been met with limited success.

3.3. Pharmacological Interventions

3.3.1. Primary prevention

Since IA can often appear very early in life, intervening prior to IA development in early childhood can be difficult.[18] Therefore, primary prevention trials have targeted first degree relatives with high genetic risk in *HLA* Class II genes which account for over 50% of genetic risk for T1D.[98] Most individuals with T1D have high risk *HLA* haplotypes *DR4* or *DR3,* but not all people with these high risk genes go on to develop T1D.[28,99,100] These observations suggest that environmental antigens may also play a role in development of islet autoimmunity and T1D. Oral insulin antigen studies showed that daily oral administration of 67.5 mg of insulin, compared with placebo, resulted in an immune response without hypoglycemia.[101] Follow up studies confirmed safety of oral insulin in infancy but unfortunately did not confirm a protective immune response.[102].

3.3.2. Secondary prevention

Additional studies have been directed towards delaying progression in people with detectable IA (Stage 1 or 2). Many of these studies have focused on antigen specific therapies such as parenteral insulin, oral insulin and GAD. [103–106] The Diabetes Prevention Trial, Type 1 (DPT-1) evaluated two insulin therapies in relatives with IA and dysglycemia who received low doses of insulin or placebo daily with

continuous insulin infusion for 4 days at the beginning of the study and then annually.[104] The second cohort included relatives with IA but no metabolic abnormalities who received oral insulin or placebo daily. After 6 years of follow-up, neither treatment delayed progression to clinical T1D. A post-hoc analysis showed that patients with high IAA levels who received oral insulin had delayed onset of T1D.[105] However, a follow up study by the Type 1 Diabetes TrialNet Oral Insulin Study did not confirm these findings.[107].

Immune interventions have also been explored to delay the decline in beta cell function.[108] Most notably, teplizumab significantly delays, by 2.7 years on average, the onset of stage 3 T1D in people with stage 2 T1D (IA and dysglycemia on an OGTT).[109,110] In November 2022 teplizumab was approved by the United States Food and Drug Administration to delay the onset of stage 3 T1D in adults and pediatric patients 8 years and older who currently have stage 2 T1D. Teplizumab was administered daily for 14 days via a thirty minute intravenous infusion. In the study, people with a high-risk *HLA DR4* haplotype and ZnT8A were most likely to have a response to this therapy. Notably, the numbers used for the responder analysis were small and not robust enough to guide clinical treatment decisions. Another agent recently studied in patients with stage 2 T1D is abatacept, which is a drug approved for use in polyarticular juvenile idiopathic arthritis, adult rheumatoid arthritis and adult psoriatic arthritis. Abatacept blocks co-stimulation and subsequent activation of T-cells. Abatacept was effective in preserving endogenous insulin secretion and had an effect of T-cells; however, it did not prevent the diagnosis of stage 3 T1D.[111] Low dose antithymocyte globulin (ATG) has preserved beta cell function in patients with recent onset clinical T1D, so it is now being studied in people aged 12–23 with IA, dysglycemia and markers indicating a high risk for T1D progression (NCT04291703).[112,113] Now that a clinical treatment is available, clinical trialists must find ways to continue to engage the T1D community in research trials as prevention, and not just delay of T1D onset, is the ultimate goal.

3.3.3. Tertiary prevention

Beta cell mass rapidly declines during the first few years after diagnosis, and attempts have been made to prolong the PRM utilizing immunotherapies.[85,114–119] Studies in patients with new onset T1D have attempted to target inflammation, modulate the adaptive immune response, induce tolerance with antigen specific therapies or infuse beta cell therapies. The primary endpoint in the majority of trials has been to assess the preservation of stimulated C-peptide via repeated MMTTs.[114] Thus far the most successful trial has been an aggressive course of multiple therapies of autologous nonmyeloablative stem cell transplantation (AHSCT) with granulocyte colony stimulation factor (G-CSF) for cell mobilization, and cyclophosphamide plus anti-thymocyte globulin (ATG) for induction therapy to remove activated immune cells in adults.[120–123] This intensive intervention was able to show glycemic control with current available therapies but arguably could provide more risk than benefit, especially in pediatric patients.[124].

As mentioned previously, studies using ATG and G-CSF preserved stimulated C-peptide in new onset patients with T1D one year after therapy.[115] Long term outcomes from this pilot study, 5 years after intervention those who responded to therapy demonstrated nearly unchanged HbA1c.[112] There have been other studies of immunomodulating agents with variable degrees of success. Rituximab (anti-CD20) was shown to delay C-peptide decline by 8 months in new onset patients.[125,126] Patients treated with abatacept, (CTLA-4 Ig) had a 10 month delay in C-peptide decline.[127,128] A trial in alefacept (anti-CD2) maintained C-peptide secretion, reduced insulin use and hypoglycemic events, and induced favorable immunologic profiles at 24 months.[129] Other agents to modulate immune response against interleukin-1 have had less success without preservation in residual beta cell function.[130].

Teplizumab has also been investigated in tertiary prevention with initial signs of efficacy in new onset patients.[118,131–134] However, while initial signs of efficacy in phase 2 trials showed promise, a large phase 3 trial did not meet its primary endpoint to reduce daily insulin use and improve HbA1c [118,134]. The PROTECT study (NCT03875729) is a phase 3, randomized, double-blind, placebo-controlled, multinational, multi-center study to evaluate the efficacy and safety of teplizumab, in children and adolescents ages 8–17 recently diagnosed with T1D. Results of this trial are pending, but with the recent US FDA approval of teplizumab in stage 2 diabetes, there may be an opportunity to expand teplizumab therapy to children with new onset T1D. Future T1D treatments may focus on replacing beta cells via transplantation in long standing diabetes.[135–137] Of note, at this time, only insulin preparations and amylin are approved for use by the US FDA to treat T1D.

3.4. Non-pharmacological interventions: diet and bioactive molecules

The interplay between genetic susceptibility and potential environmental triggers of T1D seems to start at a very early age. This hypothesis led researchers to look for environmental factors that act early in life, and special attention has been directed towards nutritional factors and bioactive molecules.[138].

3.4.1. Primary prevention

Primary prevention trials have focused on safe interventions in young children, who are otherwise healthy, before islet autoimmunity occurs.

3.5. Breastfeeding

The protective effect of breastfeeding against T1D has been hypothesized in 1980 s, when researchers started to collect the first evidence from animal and human studies.[139] Unfortunately, 40 years after, the disease-specific preventing proprieties of breastfeeding remains unknown, and largely debated.

Several protective mechanisms have been proposed. The increase in gut permeability, the reduction of the risk of enterovirus infections,[140] the reduction to early exposure to cow's milk proteins and related antigens, the presence of a microbial colonization of the gut with high levels of *Bifidobacterium species,*[141] a shift in the balance between tolerogenic cells and autoreactive cells and a reduction in inflammatory molecules were suggested as possible key-players in T1D prevention in breastfed infants.[142] The relative contribution of each component of the human milk (macronutrients, vitamins, oligosaccharides, minerals, immunoglobulins, lactoferrin, cytokines, long-chain poly unsaturated fatty acids, hormones, growth factors, and beneficial bacteria, etc.) is not known. The unique and dynamic composition of human milk supports and augments independently or in combination the development of immune system. and the gut microbiota and therefore could potentially contribute to disease prevention.

Current evidence regarding the effect of breastfeeding and development of T1D are derived from observational studies. One of the largest pooled analyses to assess the effect of breastfeeding on the risk of developing T1D was published in 2012.[143] The authors reviewed 43 studies including 9874 patients with T1D demonstrating a weak protective effect of breastfeeding on T1D risk (for exclusive breastfeeding $\geq$2 weeks vs <2 weeks, the OR was 0.75 (95% CI 0.64, 0.88) and for exclusive breastfeeding $\geq$ 3 months vs < 3 months, the OR was 0.87 (95% CI 0.75, 1.00)).

In 2017 data from two large population-based cohorts of a total of 155.392 Danish and Norwegian children revealed that the risk of T1D doubled in those who were not breastfed. No significant difference was observed upon comparing the duration of breastfeeding.[144] In 2021 the TEDDY study groups examined the optimal duration of breastfeeding for T1D prevention. A large cohort of children with increased genetic susceptibility for T1D and celiac disease was followed from birth to 2 years of age and monitored for the earliest signs of autoimmunity. The

authors found that breastfeeding duration beyond 6 months and exclusive breastfeeding longer than 3 months were not associated with protection from developing autoimmunity associated with T1D.[145] More recently a systematic review and meta-analysis synthesized the current knowledge on diet and incidence of T1D. The authors concluded that longer durations of any or exclusive breastfeeding were inversely associated with T1D. The largest risk reduction was observed for 6–12 months versus < 6–12 months of any breastfeeding (RR: 039, 95% CI 026–058, I2 =43%).[146].

Based on the available evidence, to date, the effect of human milk on T1D prevention remains inconclusive. Nevertheless, evidence supporting its role in prevention is increasing.[147] Therefore, breastfeeding should be encouraged in children at risk of T1D, as for the general population, due to other established benefits. There is a need to perform prospective studies in large population samples.

3.6. Infant formula and cow-milk proteins

The link between T1D development and early introduction of cows' milk proteins was suggested by findings from epidemiological, animal, and human studies in the 1990 s [148–151] These studies showed an association between early cows' milk consumption and the incidence of T1D and an increased prevalence of antibodies against cows' milk proteins and insulin-binding antibodies in new-onset T1D children.[152] Following these observations, a number of studies tried to provide the mechanism whereby the early assumption of cows' milk proteins could lead to T1D. Potential pathogenic factors identified include =similarities in the amino acid sequence of cows' milk proteins with parts of high T1D risk HLA chains, resulting increased intestinal permeability, and inflammation of the intestinal mucosa and modification of the gut microflora in children fed cow-milk proteins.[60,153].

Several trials were designed to determine if T1D could be prevented by giving babies hydrolyzed infant formula.[148,149,154,155] In 2010 Knip at al, reported weaning infants to an extensively hydrolyzed formula was associated with a decrease in the frequency of IA by the age of 7.5 years.[156] This study remains the only study showing that reduced exposure to cow-milk protein in the infant diet can prevent T1D in a genetically high-risk population. The TRIGR trial conducted on 2159 genetically high-risk children from 15 different countries clearly showed that weaning to a hydrolyzed formula compared with a conventional formula during the first 6–8 months of life did not reduce the cumulative incidence of T1D after median follow-up for 11.5 years.[157] Because this study negated the hypothesis that cow's milk proteins play a critical role in the development autoimmune diabetes, there is no evidence to revise the current dietary recommendations for infants at high risk for T1D.

3.7. Complementary feeding and gluten

Evidence from systematic reviews indicates that initiating complementary feeding before 3–4 months of age is associated with higher risk of several diseases. Regarding T1D, the risks of solid foods included in a weaning regimen have been explored in few studies; therefore, evidence is limited, discordant or inconclusive.[158–160].

The Type 1 Diabetes Prediction and Prevention Project (DIPP), a prospective cohort study, aimed to evaluate the effect of complementary foods introduction on beta cell autoimmunity. More than 3000 newborn babies with genetic susceptibility to T1D were periodically screened for IA until 12 months of age. The study revealed that early introduction (between 3 and 4 months) of fruit, berries and roots was associated with a higher risk to develop β cells autoimmunity.[161] These results were not replicated by other studies. To the best of our knowledge, no randomized controlled trials have been designed to test the hypothesis that delaying the introduction of certain foods has a beneficial role in preventing T1D.

In *vitro*, in *vivo* and human studies have suggested that gluten can increase proinflammatory cytokines and induce dysbiosis of the gut microbiota.[162] The relationship between gluten and T1D was firstly explored several years ago with conflicting results.[144,159,160, 163–165] The available studies were all observational, focusing on high-risk populations and mainly directed to investigate both the effect of an early introduction of gluten and the gluten intake amount on the risk of developing T1D.

A recent metanalysis showed that later introduction to gluten (3–6 versus <3–5 months) was associated with reduced T1D risk (RR: 036, 95% CI 017–075, I2 =0%) with a similar tendency for cereal introduction but no association was found for IA. Authors concluded that the heterogeneity was high, and the certainty of this evidence was low. [146].

3.8. Micronutrients

The immunomodulatory proprieties of calcitriol have been extensively studied, and the immunomodulatory effects of vitamin D are particularly relevant in T1D where calcitriol exerts activities on dendritic cells, macrophages, CD8 + and CD4 + T cells, and B lymphocytes. [166] Compelling evidence from NOD mice showed that mice treated with oral calcitriol experienced a significantly delayed T1D onset. Also, a significant inverse association between circulating 25(OH)D concentrations in humans and the risk of T1D have been reported. Together, these findings have encouraged the development of studies using calcitriol as a T1D preventative agent in children.[167–170].

In a large birth cohort study, vitamin D supplementation was associated with a decreased frequency of T1D. Children who regularly took 2000 IU daily of vitamin D had a relative risk of 0.22 (0.05–0.89) compared with those who regularly received less than the recommended amount.[171] The most recent meta-analysis supports these results and showed that vitamin D intake during early childhood is significantly associated with a reduced risk of T1D.[172] However, the current evidence is observational because adequately powered, randomized controlled trials with long periods of follow-up are lacking. Moreover, given the heterogeneity of studies published so far, the best formulation, dose, and duration of calcitriol supplementation is unknown.

Because vitamin A can modulate the adaptive and innate immune response, there is growing interest in examining the potential role of vitamin A in T1D. A recent review reported that in animal studies both vitamin A and all-trans retinoic acid effectively induced immune tolerance and protected beta cells against autoimmune islet inflammation and progression to diabetes.[173] Currently no data are available in humans.

Oxidative stress is implicated as playing a role in the pathogenesis of T1D, as well as in the development of complications. Based on this assumption, the dietary antioxidants vitamin C, vitamin E, zinc and selenium may play a preventive role in this disease.[174] TEDDY examined plasma ascorbic acid up to 6 years of age and found that higher plasma ascorbic acid levels may protect from IA development, but not from T1D risk progression.[175] Considering vitamin E, zinc and selenium, no trials have been published on the effect of a diet rich of these micronutrients for the prevention of T1D.

3.9. Probiotics

Gut microbiota are implicated in T1D pathogenesis through multiple and complex mechanisms which involve modulation of tolerance to dietary antigens, intestinal inflammation and gut permeability.[176] Given the influence of dysbiosis on the development of T1D, Human studies have demonstrated the efficacy of probiotics in increasing the expression of junction and adhesion proteins of the intestinal mucosa with improvement of barrier functions, reducing oxidative stress, and modulating the inflammatory response with an increase in T lymphocytes and anti-inflammatory cytokines.[138].

Studies examining the effect of probiotic supplementation on

prevention of beta cell-autoimmunity and T1D onset show mixed results. TEDDY showed a positive association between probiotic supplementation within the first 27 days of life and the prevention of beta cell-autoimmunity.[177] In contrast, in a study by Savilahti et al., no correlation was found between probiotic supplementation in genetically high risk infants and the development of autoimmunity within 5 years or with progression to T1D within 13 years.[178].

In summary, definitive conclusions on the contribution of nutritional factors and bioactive molecules in preventing or delaying the onset of T1D is extremely challenging. Most of the current evidence comes from observational studies. Marked heterogeneity and biases are frequently reported as main limitations of the available studies. Nutritional factors and bioactive molecules may act simultaneously given the mutual interplay between gut and diet making it difficult to determine what is causing the primary protective effect. Finally, long-term follow-up studies are lacking. Based on the current knowledge, not enough evidence exists to revise current dietary recommendations for infants at high risk for T1D to prevent the disease onset.

3.10. Optimal timing for intervention

T1D is characterized by marked heterogeneity relating to the risk for development of IA, progression through preclinical stages, and clinical onset.[51] Despite this heterogeneity, it remains important to identify individuals early enough to allow the opportunity for prevention of T1D or a delay in the destruction of beta cell mass.

Removing the exposure to environmental factors which act as *primum movens* in T1D pathogenesis would be the optimal treatment strategy and would likely need to occur very early in life. However, this approach to disease prevention is not feasible based on the available knowledge of T1D pathogenesis and the absence of an unequivocal association between an environmental determinant and T1D onset. Therefore, the best strategy remains to identify individuals with IA (stage 1 and 2) as these individuals still have functioning beta cells that can be preserved. Identification of people with early stages of T1D will allow further study of the determinants of T1D progression, entry of people into T1D prevention trials and identify individuals who are eligible for clinical treatments (i.e., teplizumab).

Screening family members of people with T1D for IA as recommended by the American Diabetes Association remains important.[179] In addition, screening patients found to have glucose abnormalities incidentally or during an acute illness, children with another autoimmune condition, and children with a genetic syndrome putting them at high risk for autoimmune disease (e.g. Turner syndrome, Trisomy 21, Noonan Syndrome, Klinefelter's Syndrome) may also yield detection of individuals with early stages of T1D. In recent years, research based general population screening programs using IA alone or in combination with genetic risk factors have also been established.[180,181] Within the Fr1da-study, 100.000 preschoolers were tested for the presence of multiple IAs by primary care pediatricians. Children tested positive and their parents were invited to participate in an education and counselling programme at a local diabetes centre. Anxiety, depression and burden of diagnosis at pre-symptomatic stage of disease were also assessed. After this first experience, the Fr1da-Plus-Study extended screening to older ages (9.0–10.99 years),and follows children with single IA for up to 3 years for progression to multiple islet autoantibody positivity (ongoing). The Fr1da studies were the first studies which examined the feasibility of early diagnosis of T1D, without preselecting the target population in terms of family history and genetic risk. This study demonstrated the feasibility of collaborating with primary care pediatricians and open the door to public health screening tests within the context of regular checkups and counselling activities.

Finally, many factors need be considered when determining the ideal timing of an intervention. First, the feasibility and the acceptability screening for IA is vitally important. In addition, the psychological outcomes of participating in screening and interventions for families and children should be considered. Finally. the long-term costs and savings should be calculated given that a person with T1D loses an average of 32 years of healthy life.

4. Conclusion

T1D is an incredibly complex disease. Although the pathogenic environmental trigger and the rate of progression through T1D stages are not yet fully understood, the identification of early T1D with the measurement of IA is possible. With the ability to identify those at high-risk for T1D development, there is hope for the prevention of T1D. The recent FDA approval of teplizumab to delay the onset of T1D marks an impressive milestone in diabetes research and in clinical care. Nevertheless, an intensive scientific effort is still required to develop a sustainable method of screening children and identifying which children are most likely to respond to preventative therapies such as teplizumab. Finally, the scientific community should continue to pursue new strategies to prevent progression of the T1D autoimmune process at all stages to eventually cure this complex disease.

CRediT authorship contribution statement

CM, TT, KMS: conceptualization, writing, GVZ, FC, MR reviewed and edited the manuscript.

Declaration of Competing Interest

FC, KMS are Consultants of ProventionBio. CM,TT, MR and GZ declared no conflict of interest.

Data availability

No data was used for the research described in the article.

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