

Type 1 diabetes: A predictable disease

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Abstract

Type 1 diabetes (T1D) is an autoimmune disease characterized by loss of insulin producing beta cells and reliance on exogenous insulin for survival. T1D is one of the most common chronic diseases in childhood and the incidence is increasing, especially in children less than 5 years of age. In individuals with a genetic predisposition, an unidentified trigger initiates an abnormal immune response and the development of islet autoantibodies

directed against proteins in insulin producing beta cells. There are currently four biochemical islet autoantibodies measured in the serum directed against insulin, glutamic decarboxylase, islet antigen 2, and zinc transporter 8. Development of islet autoantibodies occurs before clinical diagnosis of T1D, making T1D a predictable disease in an individual with 2 or more autoantibodies. Screening for islet autoantibodies is still predominantly done through research studies, but efforts are underway to screen the general population. The benefits of screening for islet autoantibodies include decreasing the incidence of diabetic ketoacidosis that can be life threatening, initiating insulin therapy sooner in the disease process, and evaluating safe and specific therapies in large randomized clinical intervention trials to delay or prevent progression to diabetes onset.

Key words: Autoimmunity; Autoantibodies; Diabetes prevention; Screening; Type 1 diabetes

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Core tip: Type 1 diabetes (T1D), the immune mediated form of diabetes, is now a predictable disease with the measurement of islet autoantibodies. The presence of two or more antibodies defines preclinical disease as nearly everyone with multiple antibodies progresses to clinical diabetes. With improved platforms to measure islet autoantibodies, screening the general population is now a goal. Early identification of preclinical diabetes allows for less diabetic ketoacidosis, early initiation of insulin therapy, and the potential to delay or prevent diabetes onset. Clinical trials using safe and specific therapies to block disease specific immune cells are underway in T1D.

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INTRODUCTION

Type 1 diabetes (T1D) is a chronic disease caused by immune-mediated destruction of insulin producing beta cells in the pancreas^[1]. The destruction of beta cells results in insulin insufficiency, and patients develop life-threatening hyperglycemia that clinically manifests with weight loss, polyuria, and polydipsia. The majority of patients who develop T1D have high-risk human leukocyte antigen (*HLA*) genes. Islet autoantibodies can be measured in the serum of these high-risk individuals years before the onset of any clinical symptoms, making T1D a predictable disease. Multiple prevention trials in patients with high-risk *HLA* genes or in patients who have measurable autoantibodies have been completed. To date, no trial has prevented the onset of T1D, but data indicates that the disease process may be delayed by administering oral insulin to induce insulin specific regulatory T-cells in the gut, resulting in decreased inflammation in the pancreas. This review summarizes the epidemiology, risk factors and pathogenesis of T1D. The review also examines the goal of screening the general population for T1D risk and preventing disease onset in individuals with preclinical disease.

EPIDEMIOLOGY

T1D is one of the most common chronic diseases in childhood and is diagnosed at an increasing rate in adults. The incidence rate varies significantly by geographical region. Sweden, Finland, Norway, United Kingdom, and Sardinia have the highest incidence of T1D at an age-adjusted rate of > 20/100000 patient years. For comparison, the United States has an incidence rate of 17.8/100000 patient years in a predominantly Caucasian population. China and South America have the lowest incidence of T1D, reported as < 1/100000 patient years^[2-5]. The rate of T1D diagnosis is increasing in most countries, with rates dramatically increasing in children less than 5 years of age^[6]. The annual incidence of T1D is increasing globally by 2.3% per year and is estimated to be increasing by 2.7%-2.8% in non-Hispanic white youth in the United States^[7]. Large registries in both Europe and the United States show that the incidence of T1D peaks between 5 to 7 years of age and again when children enter puberty^[8]. Unlike most autoimmune diseases, T1D is more common in males than females. The risk of T1D development in the general population is 1:300^[9]. In children who have a genetically related sibling, the risk is increased to 1:7 and is greatest in children under 5 years of age^[10,11]. Offspring of mothers with T1D carry approximately 3% risk and offspring of fathers with T1D carry approximately 5% risk^[12]. Genetics confer risk for development of T1D, as does seasonal variation and birth month suggesting an environmental influence on disease pathogenesis. Children born in the spring tend to be at a greater risk for developing T1D, while diagnosis is increased during climatically cold

seasons^[13-16]. This is an epidemiological association that requires further investigation.

RISK FACTORS

Genetic

T1D is a polygenic disorder with many genes contributing varying amounts of genetic risk for disease development. The genes conferring risk for diabetes are generally classified as *HLA* and *non-HLA* genes. Large genome wide association studies show that over 40 genes increase susceptibility to T1D^[17,18]. The major determinant of genetic susceptibility to T1D, contributing greater than 50% of the genetic risk, is conferred by genes in the *HLA* complex located on chromosome 6^[9]. The *HLA* complex is divided into 3 regions: classes I, II, and III. Alleles of the class II genes, *DQ* and *DR* (and to a lesser extent *DP*), are the most important determinants of T1D. These class II molecules are expressed on antigen-presenting cells (macrophages, dendritic cells, and B cells) and present antigens to CD4 T lymphocytes. *DQ* and *DR* genes are in close linkage disequilibrium on chromosome 6 with specific *DQ* and *DR* genes inherited together. The presence of the *DR4/DQ8* haplotype increases the odds ratio for T1D development to approximately 11, indicating an individual with this haplotype is 11 times more likely to develop T1D than those without. Approximately 90% of all individuals with T1D have either or both the *DR4/DQ8* or *DR3/DQ2* haplotypes. Interestingly, *HLA* genes also confer protection from T1D development. Individuals who have the specific *DQ6* allele (*DQB1*06:02*) are dominantly protected from T1D, with an odds ratio of 0.03 for disease development^[19].

Of the *non-HLA* genes, insulin and protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) confer risk for T1D development but to lesser degrees than *HLA* genes^[20]. Similar to *HLA* class II genes, insulin gene polymorphisms can confer both susceptibility to and protection from T1D development. At the 5' end of the *insulin* gene, there are variable numbers of tandem repeats. Having more repeats correlates to more insulin message being expressed in the thymus. The thymus responds by developing central tolerance to insulin. In individuals with fewer repeats, autoreactive T-cells can persist, and the risk for T1D development is increased^[21]. *PTPN22* helps regulate antigen receptor signaling and T cell activation, and a single nucleotide polymorphism (arginine to tryptophan at position 620) has been associated with a number of autoimmune disorders including T1D. A gain of function polymorphism decreases T cell receptor signaling which confers diabetes risk. It is unknown why decreased T cell activation leads to T1D risk, but it can be hypothesized that deficient negative selection of thymic cells may be involved^[22,23].

Environment

Genetics alone does not lead to T1D; the environment also plays a pivotal role. This is evidenced by the fact

that not all individuals with high-risk genes develop T1D. In fact, the majority of individuals with high-risk HLA class II genes (DR4/DQ8 and DR3/DQ2) do not develop T1D. There are likely one or more environmental factors that trigger and perpetuate the autoimmune disease process prior to hyperglycemia and a clinical diagnosis of hyperglycemia and T1D. Large natural history studies indicate that the development of islet autoantibodies (the first laboratory evidence of beta cell autoimmunity) in high-risk individuals often occurs between 9 mo and 2 years of age^[24]. This suggests that an environmental trigger is present early in life, possibly *in utero*.

One of the most extensively evaluated environmental triggers is viral infection. Many viruses are implicated in the development of T1D including enteroviruses such as coxsackie B virus, cytomegalovirus, congenital rubella syndrome, and rotavirus^[25-32]. Enterovirus is the leading candidate for contributing to T1D development. Epidemiologic studies in Finland show that the development of beta cell autoimmunity parallels the seasonal pattern of enterovirus infection and clinical symptoms of enteroviral infection^[33,34]. Enterovirus infection was strongly associated with the development of autoantibodies in the Diabetes Autoimmunity Study in the Young (DAISY) cohort^[35]. Laboratory evidence of enterovirus infection is reproducibly present in individuals with new onset T1D, pregnant women whose children develop T1D, and donor pancreata of individuals with T1D^[36,37]. The exact mechanism of how viruses induce autoimmunity is not clear. The molecular mimicry hypothesis proposes that because the P2-C protein sequence of enterovirus is similar to glutamic decarboxylase (GAD), which is expressed in islet cells, the immune system erroneously targets destruction of beta cells^[38]. The other leading hypothesis is that viral infection activates autoreactive T cells. As evidence, Cytomegalovirus B4 has tropism for pancreatic tissue and infection results in release of beta cell antigens that are phagocytized by macrophages and presented to autoreactive T cells^[39].

Another potential environmental influence relates to the north-south division of diabetes development in the world, with a higher incidence of T1D in northern climates compared to southern. The north-south hypothesis implicates that a lack of vitamin A and/or D exposure early in life predisposes individuals to the development of autoimmune diseases including T1D. Offspring of mothers supplemented with vitamin D during pregnancy and young children supplemented with vitamin D have shown a reduced risk of T1D development that may be dose responsive^[40,41]. However, an analysis from the DAISY Study found that vitamin D intake and 25(OH) vitamin D levels throughout childhood were not associated with the development of islet autoantibodies or T1D development^[42].

Early introduction of cow's milk and gluten have also been extensively studied. The introduction of gluten into an infant's diet prior to three months and after 7 mo has been associated with increased autoantibody development^[24,43]. Some studies also indicate

that breastfeeding or using elemental formula may be protective against T1D. Other environmental factors that continue to be explored include nitrosamine compounds, maternal age, pre-eclampsia, and childhood obesity. There is no evidence to suggest that vaccines increase the risk of T1D development^[44]. To date, there are no causal environmental factors that trigger the development of islet autoantibodies or increase the risk of progression to clinical T1D development. However, there is a large international prospective longitudinal study, The Environmental Determinants of Diabetes in the Young, currently underway to evaluate potential environmental factors in T1D^[45].

NATURAL HISTORY

Three decades ago, it was hypothesized that T1D is a chronic autoimmune disorder that develops in stages, and the model remains valid today (Figure 1). In genetically predisposed individuals (those with DR4/DQ8 and/or DR3/DQ2 haplotypes) there is an environmental trigger that leads to a break in immunologic tolerance and loss of beta cell mass. Over a period of time, usually years, there is autoimmune destruction of insulin producing beta cells that is marked by the presence of serum islet autoantibodies (Figure 2). As the process continues, very likely in a relapsing and remitting manner, there is a loss of glucose stimulated insulin release, and eventually insulin deficiency such that overt hyperglycemia results and clinical T1D is diagnosed^[4].

How an inciting event leads to an aberrant immune response is not completely understood. Most hypotheses focus on immunologic abnormalities in antigen presentation by HLA molecules to T cells in the thymus and peripheral lymph organs. T cells are educated in the thymus to self-antigens, such as insulin, and if there are dysregulated immune processes, self-reactive T cells can escape central tolerance and exist in the periphery^[46,47]. Once these cells encounter their target antigen or peptide in peripheral lymph organs, they become activated to target beta cells. Other hypotheses focus on environmental triggers leading to immune activation and targeting of beta cells. The molecular mimicry theory proposes that a viral or bacterial protein shares amino acid sequence homology with beta cells and induces immune system activation through targeting beta cell antigen that is molecularly similar to a foreign antigen^[38]. Finally an infectious triggering event may allow beta cells to become more sensitive to cytokine and free radical induced inflammation^[48].

Recently the network for pancreatic organ donors has been established to study the pancreata of deceased donors with islet autoantibodies (preclinical disease) or established T1D^[49]. The goal is to understand mechanisms of disease pathogenesis and interactions between beta cells and the immune system^[50]. What we have gleaned from the initial efforts is that islet infiltrates (insulinitis) are present in a lobular pattern in the pancreas, and there is a predominance of CD8 and CD4 T cells,

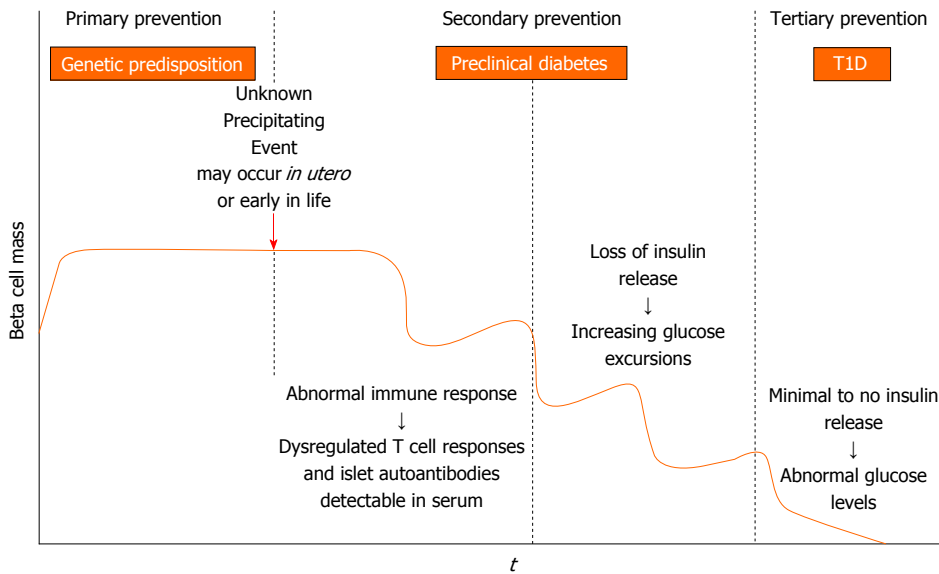


Figure 1 Stages in the development of type 1 diabetes adapted from the initial model proposed by George Eisenbarth. In genetically at risk individuals an unknown trigger, presumably environmental, initiates an autoimmune response that results in loss of beta cell mass. Before metabolic disturbances occur, islet autoantibodies (insulin, glutamic decarboxylase, islet antigen 2, zinc transporter 8) are measurable in serum. As beta cell mass decreases, potentially in a relapsing-remitting manner, there is loss of endogenous insulin release and ensuing hyperglycemia. Within this model, there are opportunities for type 1 diabetes (T1D) prevention in genotypically high risk individuals (primary prevention) and in autoantibody positive individuals (secondary prevention). Interventions to preserve remaining beta cell mass at diagnosis are also possible (tertiary prevention).

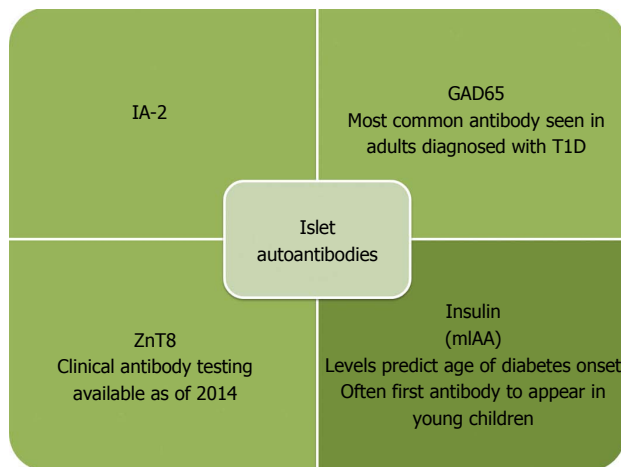


Figure 2 Insulin autoantibodies are often the first antibody to develop in young children. In contrast, adults most often are GAD65 and IA-2 autoantibody positive at diagnosis. The ZnT8 antibody is the most recently identified autoantibody with commercial testing now available. T1D: Type 1 diabetes; GAD65: Glutamic decarboxylase; IA-2: Islet antigen 2; ZnT8: Zinc transporter 8.

B-lymphocytes, and macrophages^[51,52]. Pancreata from established T1D patients also show an overall decrease in weight compared to age matched controls, potentially related to atrophy of the exocrine pancreas with the loss of beta cells^[52]. The first serological evidence of an autoimmune response to beta cells is the appearance of autoantibodies to insulin (IAA), GAD, islet antigen 2, and zinc transporter 8^[53]. Placental antibodies are no longer present after approximately 6 mo, so any antibodies in serum after that time reflect endogenous antibodies. If an individual develops two or more of these antibodies, they will eventually progress to clinical onset of T1D^[54].

Approximately 90% of individuals have two or more islet cell autoantibodies at diagnosis, and it is likely that the remaining 10% of individuals (islet autoantibody negative) have autoantibodies against antigens that have yet to be discovered. In children, IAA is usually the first antibody to develop, and the progression to T1D is 100% in children with a persistently high level of IAA^[55,56]. This is in contrast to adults who tend to have higher levels of GAD at diagnosis. Islet autoantibodies can be easily measured in the serum, with the gold standard method for detecting antibodies being fluid phase radioimmunoassays (RIA)^[57]. More recently, islet autoantibodies are now able to be measured from smaller volumes of serum and without the use of radioactivity using electrochemiluminescence as a detection method while maintaining similar sensitivity and specificity to RIA^[58,59]. The rate at which individuals with positive islet autoantibodies progress to clinical T1D is dependent upon the age of appearance, insulin autoantibody level, and the number of autoantibodies present^[55]. Hemoglobin A1c rises 1 to 1.5 years prior to diagnosis. Therefore, reduced insulin secretion and resultant hyperglycemia occur before T1D is clinically diagnosed^[60,61]. Once T1D is clinically diagnosed, individuals must commit to lifelong blood glucose monitoring and intensive insulin administration *via* multiple daily injections or an insulin pump to achieve good glycemic control. With improved diabetes management, the risk for long-term complications such as renal failure, myocardial infarctions, stroke, and lower extremity amputations has decreased over the last two decades^[62]. However despite the decreasing prevalence of complications in diabetes, the need still exists to understand the underlying pathogenesis of complications such as diabetic cardiomyopathy and

novel approaches for treating complications such as neovascularization in diabetic foot disease^[63,64].

SCREENING AND PREVENTION

The American Diabetes Association recently adapted their guidelines to recommend screening for islet autoantibodies in high-risk individuals^[65]. Highly sensitive serological assays are not widely available, and all screening is recommended to be done in the setting of a clinical research study. To date, general population screening has been done through large clinical trial networks such as the National Institutes of Health sponsored TrialNet, which enroll and screen first or second degree family members of individuals with T1D. By identifying individuals with positive islet autoantibodies, the rate of diabetic ketoacidosis (DKA) at diagnosis is reduced^[66]. Preventing DKA is important as altered mental status, coma, and even death can occur^[67]. In fact, DKA is the most common cause of death in children with T1D^[68]. Without screening, DKA at diagnosis is relatively common^[69]. In the EURODIAB study, 42% of children presented in DKA (pH < 7.3) at the time of diagnosis with T1D^[3]. By identifying individuals with positive autoantibodies, insulin therapy can be initiated early, and these children can enroll in studies aimed at preserving beta cell mass. In adults, maintaining endogenous insulin secretion reduces hemoglobin A1C, reduces the risk of severe hypoglycemia, decreases reliance on exogenous insulin, and decreases the rate of long-term complications^[70-77]. In children, there has been very little data collected regarding residual beta cell mass beyond the first year after diagnosis^[78-82]. A case-control study did show that children without severe hypoglycemia had increased residual beta cell mass compared to those children with severe hypoglycemia^[83]. An effective method of preserving beta cell mass is not yet available, and the benefit of increased residual beta cell mass in children remains to be confirmed.

According to the World Health Organization's principles of early disease detection, T1D is a condition that meets criteria for the establishment of a screening program. These principles include the condition is an important health problem, there is a recognizable latent stage of the disease, the natural history of the disease is understood, there is an adequate and accepted laboratory screening test, providers agree on who should receive treatment and there is a treatment available, there are adequate resources for diagnosis and treatment, and the cost of overall medical care would not increase^[84]. Islet autoantibodies can be reliably measured in serum, with each antibody assay having a specificity of 99% when measured by radioimmunoassay in tertiary referral centers such as the Barbara Davis Center for Diabetes. The sensitivity for each autoantibody assay ranges from 70%-80%. We view these radioimmunoassays as a confirmatory test for T1D. A desired screening test needs to be reliable with high sensitivity, cost effective, and technically feasible, likely as a multiplex assay in

which all four autoantibodies are measured in a single well of an assay plate. Currently, to measure islet autoantibodies a blood draw is required with subsequent shipping of venous or capillary blood samples to a reference laboratory. This is not feasible for population wide screening due to technical requirements of sample collection and high cost. Screening large populations of infants for metabolic diseases and other congenital disorders has been successfully done using dried blood spots^[85]. To establish an accepted screening program for T1D, the sensitivity and specificity of islet autoantibodies, specifically insulin autoantibody, needs to be established using a feasible collection method such as dried blood spots on filter paper, which would be a simplified collection method and more cost effective. Overall, T1D would not be over diagnosed with general population screening as diagnosis of the disorder requires both the presence of islet autoantibodies and metabolic abnormalities.

Ideally, individuals who screen positive for islet autoantibodies can be offered a treatment to prevent or delay the progression to T1D. Many secondary prevention trials have been completed with more currently underway^[86]. As population based screening may be feasible in the near future, it is important to continue secondary prevention trials with the goal of delaying or preventing progression to T1D in islet autoantibody positive individuals. Patients enrolled in clinical intervention trials benefit from close follow up by medical professionals, early diagnosis of T1D, decreased incidence of DKA, and early initiation of insulin therapy (Figure 3).

Secondary prevention trials

As T1D is a predictable disease with the measurement of islet autoantibodies, it logically follows that the disease should be preventable. To date, the majority of secondary prevention trials (enrolled individuals with preclinical disease) have administered different preparations of insulin to autoantibody positive individuals in an attempt to slow the progression to T1D onset^[87]. The first such trial was the diabetes prevention trial-type 1 in which at risk patients were either administered subcutaneous insulin or oral insulin in randomized, double-blinded, placebo controlled trials. Oral insulin has no metabolic effect; however, orally administered insulin does encounter mucosal gut-associated lymphoid tissue. The role of this lymphoid tissue is to provide protection from orally acquired pathogens and to keep individuals from developing reactions to ingested proteins. By administering low doses of oral insulin, insulin-specific T-regulatory cells are produced which may release cytokines that inhibit the inflammatory cascade that leads to β -cell destruction^[88-90]. Relatives of patients with T1D who were 3 to 45 years of age and had high-risk *HLA* genes and one or more positive autoantibodies were evaluated for abnormal glucose metabolism. Those individuals who had abnormal glucose tolerance ($n = 339$) were administered 0.25 units/kg per day of Ultralente insulin twice daily and received an intravenous insulin infusion for four

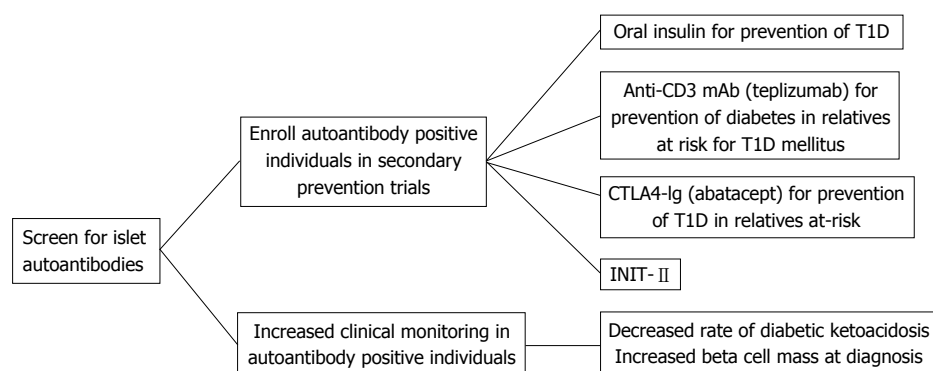


Figure 3 The measurement of serum islet autoantibodies has made type 1 diabetes a predictable disease. Early identification of islet autoantibody positive individuals leads to improved clinical outcomes by decreasing the risk for diabetic ketoacidosis and potentially preserving beta cell mass through clinical prevention trials. T1D: Type 1 diabetes; INIT- II: Intranasal Insulin Trial.

days at the beginning of the study and then annually. There was no effect of low-dose subcutaneous insulin on delaying the progression to T1D^[91]. Participants with normal glucose tolerance received 7.5 mg/kg per day of oral insulin ($n = 372$). An oral glucose tolerance test was completed every 6 mo during a 6-year follow up, and there was not a delay in progression to T1D. Of interest, a post-hoc analysis showed in participants with persistently high levels of IAA (≥ 80 nU/mL) there was a delay in disease onset of approximately five years^[92]. Also, the rate of progression to T1D onset after stopping insulin was more rapid^[93]. A follow-up oral insulin trial through TrialNet is currently enrolling participants in order to determine if oral insulin can delay the progression to T1D in individuals with high IAA levels (ClinicalTrials.gov Identifier: NCT00419562).

Another insulin intervention trial from the Belgian T1D Registry identified study participants who were insulin autoantibody positive and did not have a HLA haplotype conferring protection (DQB*0602). Study participants were given two subcutaneous injections of insulin daily for 3 years ($n = 25$) or observed and prospectively followed ($n = 25$). The participants who were treated with insulin and those who refused treatment or agreed to observation developed T1D at the same rate^[94].

Many preclinical studies have suggested that administration of intranasal insulin may delay T1D development through mucosal tolerance, in which mucosal antigens have been shown to impact regulatory T cell development^[95]. To translate these findings to humans, individuals with high-risk HLA haplotypes and one or more islet autoantibodies were enrolled in the Intranasal Insulin Trial (INIT- I) ($n = 38$). This randomized, double-blinded, crossover pilot study suggested that intranasal insulin protects against the development of T1D by increasing antibody formation and decreasing T cell responsiveness^[96]. The INIT- II, a randomized, double-blinded, placebo controlled trial, is now enrolling individuals to determine if intranasal insulin can delay or prevent the progression to T1D (ClinicalTrials.gov Identifier: NCT 00336674).

However, a large study in Finland, the T1D Prediction and Prevention Trial enrolled and followed siblings of children with T1D or infants of mothers with T1D who had high-risk *HLA* genes for islet autoantibody development. Once two or more autoantibodies were detected ($n = 264$), they were randomized to intranasal insulin ($n = 137$) or placebo ($n = 127$). Interim analyses showed no benefit of intranasal insulin in delaying the onset of T1D^[97]. This indicates that intranasal insulin may not be effective at delaying diabetes onset at the administered dose and timing in the disease process. Potentially insulin antigen specific therapies may need to be administered earlier in the disease course to have an impact on delaying progression to T1D.

Several trials using non-antigen specific therapies including bacille calmette-guerin injections, Ketotifen (histamine antagonist), oral cyclosporine, and nicotinamide (B6) have been completed. No study has prevented or delayed T1D development^[98-104].

Clinical trials with drugs aimed at modulating the immune response and preserving endogenous insulin secretion in patients with new-onset T1D are termed tertiary prevention trials^[51]. Only recently have these drugs expanded to prevention trials in islet autoantibody positive individuals (Figure 3). The CTLA4-Ig antibody (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk (ClinicalTrials.gov Identifier: NCT 01773707) and Anti-CD3 monoclonal antibody (Teplizumab) for Prevention Of Diabetes In Relatives At Risk For T1D mellitus (ClinicalTrials.gov Identifier: NCT01030861) are both TrialNet studies currently enrolling participants. Abatacept is a fusion antibody that binds to antigen presenting cells and blocks co-stimulation to T cells. Anti-CD3 monoclonal antibodies bind the CD3 molecule which is present on CD8 and CD4 T cells, thereby inhibiting T cell activation^[105]. Both of these drugs have shown some degree of success when used in new-onset trials^[106-111]. DIAPREV-IT is an antigen-based treatment currently enrolling individuals who are positive for GAD and one or more additional autoantibodies (ClinicalTrials.gov Identifier: NCT 01122446). A GAD/alum vaccine

is given at enrollment and 1 mo later. Although GAD vaccination is safe and easily administered, new-onset intervention trials have not shown long-term preservation of endogenous insulin secretion^[108,112,113].

NOVEL APPROACHES TO PREVENT T1D

Currently, insulin is the only medication approved by the United States Food and Drug Administration for the treatment of T1D. Despite T1D being a predictable chronic autoimmune disorder, there are not any therapies to preserve endogenous insulin production. As mentioned above, many large clinical intervention trials have not slowed the progression or prevented disease onset. We believe T1D will be preventable and that safe and specific therapies targeting the immune system are needed. One such approach is to target the trimolecular complex, which consists of a self-reactive CD4 T cell, insulin, and HLA molecule^[114]. It is well established that specific HLA alleles, namely HLA DQ8 which is present in approximately 60% of all T1D patients, confer significant disease risk. DQ8 is a molecular target for diabetes intervention by using small “drug-like” molecules to block antigen presentation, thereby inhibiting specific T cell activation. Preclinical studies have shown this to be a potential pathway for diabetes intervention^[115]. This concept has been advanced from bench to bedside as a clinical trial in which methyldopa (Aldomet), a clinically well-established antihypertensive drug, is being investigated to block DQ8 antigen presentation. The phase 1b dose escalation trial is using personalized medicine as methyldopa is being administered to recent onset adult T1D patients with the presence of the *DQ8* gene (ClinicalTrials.gov Identifier: NCT01883804). Methyldopa is orally administered, safe as it has been used clinically for the last 50 years, and currently indicated for the treatment of pregnancy induced hypertension. Furthermore, all individuals have three class II molecules (DQ, DR, and DP), and by blocking a single class II molecule, there are two others to permit normal immune system function.

Other approaches have targeted components of the insulin trimolecular complex including antibodies that specifically bind to an insulin peptide in the HLA molecule. Preclinical studies in an animal model of spontaneous autoimmune diabetes indicate that this approach can delay diabetes onset^[116]. Efforts are currently being made to make a human antibody, which again is a very specific immune therapy for diabetes intervention. Finally, insulin antigen specific therapy has the potential to evolve with recent advances in the field of immunology. A peptide from the insulin B chain amino acids 9-23 (B:9-23) has been extensively studied in animal models and human T1D^[117,118]. It is now appreciated that insulin B:9-23 is a key autoantigen in the disease process of both mice and humans, sharing an identical amino acid sequence in both species^[119,120]. A mutated insulin B:9-23 peptide, but not the native peptide sequence, induced protective immune responses (regulatory T cells) and prevented

diabetes onset in preclinical animal models^[121]. With a deeper understanding of how the insulin peptide binds to HLA molecules and activates T cells, an insulin vaccine again holds promise for diabetes prevention.

In conclusion, T1D is now a predictable disease with the measurement of islet autoantibodies and prevention will naturally follow. To prevent T1D, general population screening for islet autoantibodies is needed along with a safe and specific therapy for disease intervention. The genes that confer diabetes risk are now molecular targets, and tailoring therapies to specific *HLA* genes is personalized medicine. The future holds promise for delaying the progression and ultimately preventing diabetes.

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