

The Pathogenesis of Type 1 Diabetes

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Type 1 diabetes (T1D) is a chronic autoimmune disease with a metabolic outcome. Studies over the past decades, have identified the contributions of genetics, environmental factors, and disorders of innate and adaptive immunity that collectively cause β -cell killing. The risk for T1D can be genetically identified but genotypes alone do not identify factors that lead to disease progression. The incidence of T1D has been increasing in the past few decades, which may be due to reduced exposure to infections and other environmental factors that can reduce autoimmunity (hygiene hypothesis). Once initiated, the disease pathogenesis progresses through stages that have been defined on the bases of immunologic (i.e., autoantibodies) and metabolic markers (glucose tolerance). The stages only loosely capture the risk for the time to diagnosis of disease, do not directly reflect disease activity, and there may be variance in the rate of progression within stages. In a general way, the stages can be used to identify patients at risk in whom interventions may be considered to modulate progression. This was achieved with the approval of teplizumab, a humanized anti-CD3 monoclonal antibody, for delaying the diagnosis of T1D.

Over the decades since the discovery of insulin in 1922, there have been many advances in methods to replace insulin and to do so in as near a normal physiologic pattern as possible. These advances have involved new formulations of insulin with kinetics that allow more precise dosing for activity and meals, glucose monitors and continuous glucose monitoring, and delivery of insulin by continuous subcutaneous infusions. However, even when used optimally, they do not fully recapitulate the homeostasis that is achieved with pancreatic β cells, and the majority of patients, particularly children, do not achieve the standards of care that are needed to avoid the long-term complications

of the disease (Foster et al. 2019). Moreover, the uptake of these technologies has not been universal and in addition to cost, the need for continuous attention to metabolic management and its imperfections represent a lifelong burden. In addition, there is a cost in human life: For children diagnosed with type 1 diabetes (T1D), there is a 10- to 13-year loss of life expectancy even in Western countries and as much as 49 years elsewhere in the world (Gregory et al. 2022).

Insulinitis in the pancreas of patients who died with diabetes was originally described more than 100 years ago. Autoantibodies that recognized the islets of Langerhans in a patient diagnosed

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with diabetes mellitus with autoimmune polyendocrine deficiencies suggested an immune cause of these endocrinopathies (Bottazzo et al. 1974). Subsequently, activated cytotoxic T lymphocytes and other immune cells were found infiltrating the pancreas of a 12-year-old who succumbed to new-onset T1D, and indicated an immune mechanism may account for the disease (Bottazzo et al. 1985). Other immune biomarkers of the autoimmune process were identified, including antibodies against the surfaces of β cells, which were ultimately found to recognize glutamic acid decarboxylase 65 (GAD65) (Baekkeskov et al. 1990). In this review, we discuss the increasing incidence of T1D in genetically susceptible individuals and the possible contribution of environmental factors to these rates, often attributed to reduced exposures to infectious agents (i.e., the “hygiene hypothesis”). We then discuss the immunologic basis for the disease beginning with the genetic underpinnings and initiation of autoimmunity. Autoantibodies are the most frequently used biomarkers of autoimmunity, and we present how these serologic and metabolic measures define disease risk. The recognition that T1D is a progressive autoimmune disease has led to the development of clinical studies to intervene prevent the progression. Most recently, this resulted in the approval of teplizumab, a humanized FcR non-binding anti-CD3 ϵ mAb, for the delay of clinical T1D diagnosis.

TYPE 1 DIABETES IS A CHRONIC AUTOIMMUNE DISEASE THAT OCCURS IN PATIENTS WITH A SUSCEPTIBLE GENETIC BACKGROUND

There are 143 regions of the genome that are associated with susceptibility for T1D, comprising nearly 60 independent candidate genes (Robertson et al. 2021). HLA molecules are the most significant, most likely because of their ability to shape the immune repertoire—more than 90% of patients express HLA-DR3 and/or DR4. The HLA locus accounts for 40%–50% of the familial predisposition. The high-risk HLA-peptide complex is speculated to enable the development of autoreactive diabetogenic T cells

and the differentiation of regulatory T cells. In addition to central T-cell tolerance in the thymus, most likely mediated by these HLA genes as well as others such as PTPN22, there are also failures of central B-cell tolerance, which has been identified through the findings of autoreactive B cells (Kinnunen et al. 2013).

Genetic risk scores (GRSs) using microarray chips with defined alleles can improve the prediction of T1D in the general population and relatives of patients. These genetic tools are useful for identifying populations that are at increased risk and those in whom more immunologic and metabolic testing might be considered. The Illumina ImmunoChip for genotyping was shown to improve the prediction of risk for progression in autoantibody + individuals and may, therefore, identify those who should be evaluated more closely with metabolic studies (Redondo et al. 2018a). The GRS may also be useful in evaluating patients from diverse backgrounds and as a first approach for screening the general population (Bonifacio et al. 2018; Oram et al. 2022; Redondo et al. 2024).

There are also several examples of autoimmune diabetes that have developed because of mutations involving single genes that affect immune cell development, regulation, and activation that have suggested disease mechanisms. These examples (e.g., APS-1 or AIRE gene mutations, X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome [IPEX] and FOXP3 or IL-2 receptor gene mutations, and others) have shown how mutations that affect the development and functions of immune cells can lead to autoimmune diabetes (Anderson et al. 2005; Roth et al. 2018; Chaimowitz et al. 2020). More common polymorphisms (e.g., PTPN22, CTLA-4) may also affect immune cell development and function (Steck and Rewers 2011).

THE INCIDENCE OF T1D HAS BEEN INCREASING SUGGESTING THAT ENVIRONMENTAL FACTORS ARE AT PLAY

Most individuals who develop clinical T1D do not have a relative with the disease. Even among identical twins, the concordance rate is <50% and among the concordant twins, the time of

clinical diagnosis varies widely (Redondo et al. 2008; Triolo et al. 2019). The SEARCH for Diabetes in Youth Study has prospectively identified individuals <age 20 with physician-diagnosed T1D. In 2002–2012, the incidence, using 2-year moving averages, increased from 19.5/100,000 to 21.7/100,000 representing an annual increase of 1.8%/year (Mayer-Davis et al. 2017). Modeling studies have projected continued increases. Gregory et al. (2022) suggested that prevalent cases in 2040 will be 60%–107% higher than in 2021 with the greatest increases in resource-limited countries. These projected increased rates suggest that acquired or environmental factors are involved, and there are several potential mechanisms related to responses to infectious agents that may explain these findings (Fig. 1). In a recent study, the relationship between Epstein–Barr virus (EBV) and multiple sclerosis (MS) was postulated to involve a mechanism of cross-reactivity between EBV EBNA1 and Gial-CAM (Lanz et al. 2022). Likewise, in a longitudinal analysis, a very strong relationship between EBV infection and MS was found (Bjornevik

et al. 2022). Indeed, some observational studies have suggested similar relationships between enteroviruses and T1D (Dotta et al. 2007; Krogvold et al. 2015; Nekoua et al. 2022).

However, infectious agents can also suppress allergic and autoimmune disorders. In 2002, Bach suggested that the increased rates of both autoimmune and allergic diseases are best explained by the decline of infections (i.e., the “hygiene hypothesis”) (Bach 2002; Bach and Chate-noud 2012). The inverse relationships between intestinal infections as well as measles, mumps, and rheumatic fever and autoimmune diseases are striking. An illustration of the significant effect of exposure to environmental factors is seen in the rate of autoimmune diabetes among inbred nonobese diabetic (NOD) mice. In this most commonly used inbred murine model of T1D, spontaneous hyperglycemia develops in up to 75% of female mice by 30 weeks of age when the mice are housed in clean environments, whereas with conventional housing the rates rarely exceed 50%. Interestingly, more recent data have highlighted the interactions between

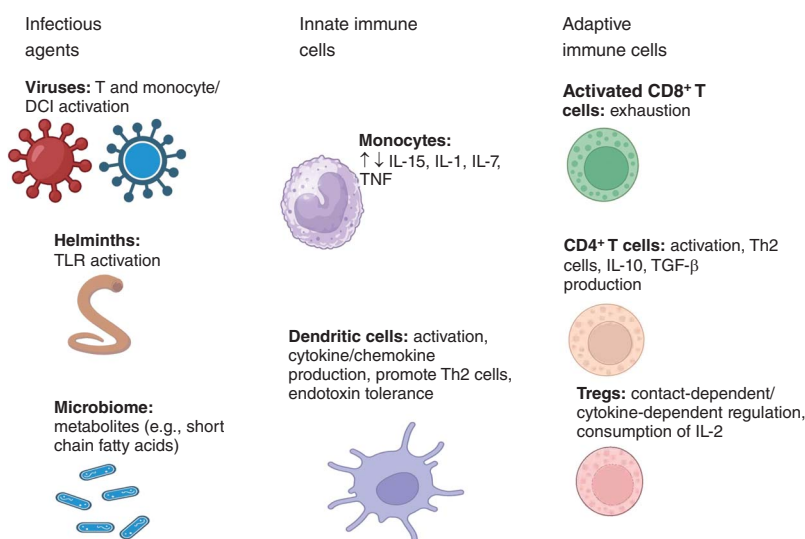


Figure 1. Infectious agents and the hygiene hypothesis. Exposure to viruses, bacteria (including the microbiome), and helminths has been postulated to reduce the development of autoimmune diseases. There are a number of mechanisms that may be involved, including nonspecific activation of T cells after viral exposure, enhancing sex steroid production or short-chain fatty acids that may have direct effects on Tregs, activation of Toll-like receptors (TLRs) by lipopolysaccharide (LPS) that is produced by bacteria or helminths, effects on antigen presentation including stimulation of immune inhibitor ligands such as IL-10 or TGF-β.

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environmental factors and innate immune signaling in triggering disease in these mice. MyD88-deficient NOD mice do not develop spontaneous diabetes when housed in a clean specific pathogen-free environment. However, germ-free MyD88-negative NOD mice develop robust diabetes, and colonization of these germ-free MyD88-negative NOD mice with a defined microbial consortium attenuates T1D (Wen et al. 2008). The rate of diabetes is about half in male mice compared to female mice, and a parallel mechanism described how commensal microbes may be responsible for increased serum testosterone that may protect male NOD mice from diabetes. It is also possible that microbiota can produce short-chain fatty acids that can affect Tregs (Brown et al. 2011; Markle et al. 2013; Kim 2018).

Similar examples of the effect of environmental factors have been observed in human communities and provide some insight into causative and protective mechanisms. The TEDDY study was designed to prospectively identify environmental factors that may be associated with progression to T1D by carefully following 8777 genetically at-risk individuals, including offspring of parents with T1D, for the relationship between acquired infections and other exposures and the acquisition of autoantibodies or diagnosis of T1D. Gastrointestinal infections and Norwalk virus exposure in the first year of life were associated with the development of insulin autoantibodies (IAAs); however, the relationship was reversed if infection occurred in the second year of life. Likewise, there was a different transcriptional immune response to enteroviruses in children under the age of 6 years, but not in children who later developed islet autoimmunity (Lin et al. 2023). Other epidemiologic data support a modulating effect of environmental factors such as socioeconomic status, place of residence (across a north/south gradient), childhood infections, sunlight, and pollutants. When comparing the gut microbiome among three genetically similar communities (Finnish, Estonian, and Russian) at the same latitude, the rates of T1D varied five- to sixfold (lowest in Russia, highest in Finland) (Vatanen et al. 2016). The characteristics of the microbiomes differ among

these three communities: *Bacteroides dorei* and other *Bacteroides* species that are highly abundant in Finland and Estonia produce lipopolysaccharide (LPS) that inhibits the immunostimulatory activity of *Escherichia coli* LPS. LPS from *B. dorei* does not protect NOD mice from autoimmune diabetes. These investigators suggest that the LPS from *B. dorei* inhibits the activation of immune cells by LPS from *E. coli* that would otherwise result in “endotoxin tolerance,” an older concept that was ascribed to a protein in rabbit sera that could confer tolerance to pyrogenic endotoxin (Kim and Watson 1965). A more recent example suggests how viral infections in humans can establish new immunological set-points that affect future immune responses in an antigen-agnostic manner that are affected by the host’s immunologic state. Male individuals who had recovered from COVID-19 had coordinately higher innate, influenza-specific plasmablast, and antibody responses after vaccination compared with healthy male and female individuals who had recovered from COVID-19. The effects of the prior COVID-19 infection were associated with higher IL-15 responses after vaccination and before vaccination, an increased frequency of memory CD8⁺ T cells (Sparks et al. 2023). Likewise, prior SARS-CoV-2 infection was associated with inflammatory cytokine profiles in patients with tuberculosis (TB) or other respiratory diseases (Cottam et al. 2023) and helminth infections have been ascribed to skewing toward Th2 responses (Méndez-Samperio 2016; Redondo et al. 2018a,b).

DATA FROM ANIMAL MODELS AND CLINICAL STUDIES HAVE DEVELOPED A GENERAL MODEL OF DISEASE PATHOGENESIS FIRST IDENTIFIED IN HUMANS BY THE PRESENCE OF AUTOANTIBODIES AND AUTOANTIGEN REACTIVE T CELLS

Insights into the earliest changes in the pancreas have been based on NOD mouse studies. Single-cell analysis showed that CD8⁺ and CD4⁺ T cells infiltrate early and there is a stepwise activation program of resident macrophages that acquire a proinflammatory state (Ferris et al. 2017).

This description of local events, largely dependent on inflammatory macrophages, may contribute to the patchy nature of insulinitis that has been observed in animal models and in patients; islets that are heavily infiltrated with immune cells can be found next to islets that are free of inflammatory cells. Other studies have localized changes to the secondary lymph nodes, including antigen presentation and even the differentiation of effector T cells from a stem-like cell pool that then migrates to the islets (Tang et al. 2006; Gearty et al. 2022). The factor(s) that trigger the conversion from stem-like to effector T cells are not clear. They may even be nonspecific, but disease progression may be limited to individuals who harbor an autoreactive repertoire or whose β cells produce inflammatory cytokines and chemokines that can drive recruitment of the immune cells to the islets (e.g., CXCL10) (Christen et al. 2003; Ejrnaes et al. 2005; Rhode et al. 2005).

With the unchecked feedforward cycle of inflammation, there are changes in β cells over time that involve the production of neoantigens such as hybrid peptides, posttranslational modifications, defective ribosomal initiation products (DRIPs), and others (DeLong et al. 2016; Kracht et al. 2017; Yang et al. 2022). Therefore, the antigens that are recognized by adaptive immune cells at the diagnosis of T1D may not be those responsible for its initiation. Interestingly, and consistent with the inflammatory events in the pancreas as initiators of islet autoimmunity, it has been observed that the volume of the pancreas may decline during the disease progression (Campbell-Thompson et al. 2019). The basis for this anatomical change has not been identified but could reflect scarring from inflammation, reduced vascular supply, or even involvement of the exocrine pancreas in the local inflammation.

AUTOANTIBODIES SERVE AS BIOMARKERS OF ADAPTIVE AUTOIMMUNITY

Genetic factors identify those at risk for developing autoimmunity and subsequently T1D, but are not useful in identifying the time of initiation or disease process. Because there is only access to

peripheral blood in humans, measures of these proposed mechanisms are only possible through the detection of autoantibodies and antigen-reactive T cells in the serum and peripheral blood. Autoreactive CD4⁺ and CD8⁺ T cells can be detected in the peripheral blood of patients following the diagnosis of disease but also before diagnosis. These cells are reactive to peptides from autoantigens such as proinsulin, GAD65, IGRP, and others as well as modified peptides, presented by T1D risk alleles (Arif et al. 2004, 2014, 2017, 2022; Gonzalez-Duque et al. 2018; Mitchell et al. 2021). However, there is not a clear threshold that can be used to identify the destructive mechanisms occurring in the pancreas using qualitative and quantitative measurements of autoreactive T cells in the peripheral blood (Arif et al. 2014; Culina et al. 2018; Ogura et al. 2018). Furthermore, the effects of biologics that target T and B cells and inflammatory mediators such as TNF- α in animal models and patients provide strong evidence for the roles of multiple subsets of immune cells in causing the disease progression (Mastrandrea et al. 2009; Jacobsen et al. 2020; Quattrin et al. 2020).

More often, the assessment of autoantibodies is used to predict disease risk. The presence of two or more autoantibodies identifies the initiation of pathogenic autoimmunity and patients who will ultimately develop T1D (Ziegler et al. 2013). These autoantibodies recognize autoantigens that are expressed by β cells. Curiously, the number of different biochemical autoantibodies rather than the titer of the autoantibodies is most closely associated with risk. Individuals in whom only a single autoantibody is detected do not have a higher risk than those with no autoantibodies.

Individuals who have autoantibodies at a younger age are more likely to progress, and progress more rapidly, than older individuals with the same autoantibody profile. The autoantibodies that are first discovered are tempered by age, and increased age at autoantibody detection is inversely related to the rate of progression. Most commonly, the first-appearing autoantibody in young children is IAAs, whereas, after age 5, glutamic acid decarboxylase autoantibodies (GADAs) appear first and the incidence of

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IAA-first declines significantly (Fig. 2). The type of the first-appearing autoantibody defines a distinct endotype in terms of genetics (IAA-first associated with DR4, GADA-first associated with DR3), transcriptomics (IAA-first associated with natural killer [NK]-cell expansion not seen in GADA-first) and rates of disease progression (Battaglia et al. 2020).

The incidence of T1D remains constant through the second decade of life and mirrors the incidence of GADA-first autoimmunity. The autoantibodies to IA2 or ZnT8 rarely appear as single antibodies, but the rate of progression from autoimmunity to T1D is markedly higher when they appear with either IAA or GADA.

Using autoantibody detection to identify the risk of diabetes is not without limitations. The autoantibodies are not direct reflections of β -cell killing, and therefore, even when adjusting for the age of detection of autoantibodies, the rate of progression to abnormal glucose tolerance and T1D is highly variable. The autoantibodies may be found for months or even years before

deterioration in glucose tolerance. While the modulating effects of age on disease progression are thought to reflect differences in immune responses between younger and older individuals, there may also be age-related differences in β cells between younger and older individuals. For example, stressed β cells have impaired processing of proinsulin and release a disproportionate amount of the prohormone compared to insulin or C-peptide (Sims et al. 2019). The ratio of proinsulin:C-peptide is increased in younger patients at risk for T1D (Sims et al. 2023). Environmental exposures have been associated with conversion to autoantibody positivity. In the TEDDY study, respiratory viruses and enteroviruses were associated with the subsequent risk of autoimmunity ($P < 0.001$) (Lönnrot et al. 2017; Lin et al. 2023). For both environmental exposure and genetics, additional analyses are needed to characterize that risk in terms of diabetes sensitivity and specificity over a defined period or at a defined age. Typically, a marker of high sensitivity has a higher false-positive rate

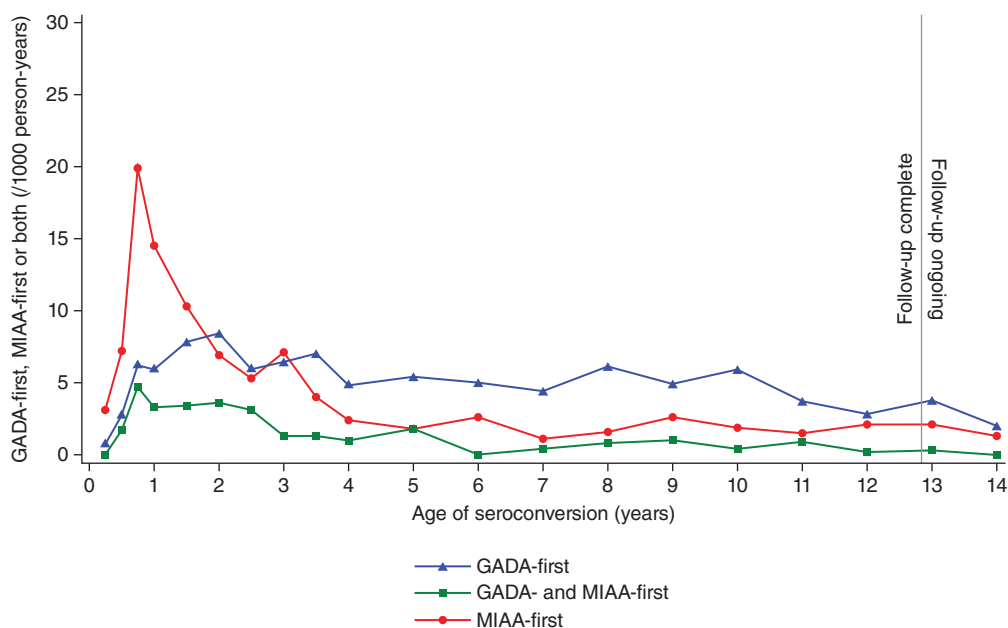


Figure 2. Incidence of islet autoantibody detection by age and type of autoantibody. The data are from the TEDDY study of relatives with and without a diabetes-affected first-degree member in children 0–15 years of age ($N = 8776$). The autoantibody incidence rate was lower among children without a diabetes-affected family member, but the pattern of appearance was exactly the same.

(lower specificity), and these factors need to be included in consideration of autoantibody screening strategies and potential interventions to interdict the disease process. Finally, it is worth recognizing that while the presence of multiple autoantibodies has 35%–50% T1D risk over 5 years and overall ~80% over their lifetime, it still means that 50% or more of individuals would not progress during a 5-year treatment period or 20% over their lifetime if left untreated.

Importantly, there are no differences between the risk or rates of progression of first-degree relatives of an individual affected with T1D and individuals with no family history (Ziegler et al. 2020). This finding, based on screening young children in the general population in Bavaria Germany, suggests that the large body of published work in a population of first-degree relatives is generalizable to the general population even though T1D incidence is significantly higher among first-degree relatives. These investigators screened with autoantibodies and found an autoantibody prevalence rate of 0.31% of the 90,632 children. This suggests that general population screening might be considered (Sims et al. 2022). To limit the number of individuals who undergo autoantibody screening, other groups have first screened for T1D risk genotypes and measured autoantibodies in those with the highest GRS.

STAGES OF DIABETES

A practical approach has been adopted to define progression through the prediabetes period into “stages” based on the detection of autoantibodies and metabolic function, which are measurements that can be used in clinical practice (Insel et al. 2015). Those who have two or more biochemical autoantibodies but normal response to an oral glucose tolerance test are classified as having stage 1 T1D. Among relatives with two or more positive autoantibodies, the 5-year progression rate to clinical T1D is 45% (Insel et al. 2015). When there is progression and impairment in glucose tolerance, indicating progressive loss of β -cell function, stage 2 T1D and the risk of progression to clinical T1D is ~50% in 2 years or

75% in 5 years. Of note, the clinical criteria for the definitions of this stage have had different definitions: For purposes of identifying individuals at high risk for the clinical diagnosis of T1D, TrialNet has used fasting, 2 hours, and intermediate glucose levels above the threshold diagnosis during a standard OGTT, whereas the ADA criteria rely on fasting and 2-hour glucose or HbA1c levels (American Diabetes Association Professional Practice Committee 2022). The evidence of the reduced β -cell mass is confirmed from clinical studies that have used these stages as enrollment criteria in prevention trials (Fig. 3). These definitions provided “mile markers” on the road to clinical T1D among those at high risk. They also serve as intermediate endpoints for clinical trials designed to interdict the disease process (Russell et al. 2023).

Stage 3 T1D refers to the fulfillment of the clinical diagnostic criteria for diabetes (American Diabetes Association Professional Practice Committee 2022). Most individuals who present with stage 3 T1D are not identified before their diagnosis and between 30% and 50% of patients present with severe metabolic decompensation—diabetic ketoacidosis (DKA). A clear benefit from identifying those with earlier stages of

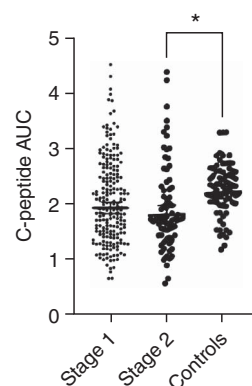


Figure 3. Stimulated C-peptide area under the curve (AUC) to oral glucose tolerance tests in patients with preclinical type 1 diabetes (T1D). Patients enrolled in a trial with stage 1 T1D (from the TrialNet TN18 study), stage 2 T1D (from the TrialNet TN10 study), or matched autoantibody controls underwent OGTTs ($P < 0.05$ by ANOVA). (Figure based on data in Herold et al. 2019 and Russell et al. 2023.)

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T1D is the avoidance of DKA, which has a 4.5% mortality (Ramphul and Joynauth 2020).

PROGRESSION OF DIABETES AFTER CLINICAL DIAGNOSIS

Despite the metabolic decompensation that results in the diagnosis, the majority of patients with stage 3 T1D still retain significant levels of endogenous β -cell function (Steele et al. 2004; Greenbaum et al. 2012). Most patients have a stimulated C-peptide level of at least 0.2 pmol/mL, which has been shown to represent a threshold with reduced risk of secondary end-organ complications if the level can be maintained (Palmer et al. 2004).

Provocative tests are used to assess β -cell function. Before the diagnosis, the response is measured during an oral glucose tolerance test by the levels of C-peptide that is cosecreted with insulin by pancreatic β cells. After the clinical diagnosis, a mixed meal tolerance test is more frequently used, which uses a liquid meal with protein and carbohydrate to enhance β -cell responses. Clinical trials generally use the area under the C-peptide response curve as a trackable measure.

For most patients, there is a progressive decline in function over time. In the first 2 years after the diagnosis, this rate has been estimated, from control participants in TrialNet studies, using a mixed meal tolerance test, to be -0.0245 pmol/mL/month (95% CI -0.0271 to -0.0215) in the first 12 months and -0.0079 pmol/mL/month (-0.0113 to -0.0050) in month 12–24 (Greenbaum et al. 2012). As in the prediagnosis period, the rate of decline varies by age and is slower for those $>$ age 21 but with variance across all ages. Overall, at 2 years after diagnosis, 12% of patients ($n = 191$) had $<7.5\%$ decline in the stimulated C-peptide response compared to the time of diagnosis. In the Joslin Medalist Study, which is a follow-up of patients with T1D of more than 50-year duration, detectable C-peptide levels were found in 67.4% of patients. However, other studies have confirmed a more universal decline (Keenan et al. 2010). Data from the EDIC trial, that has followed 944 patients from the Diabetes Control and Compli-

cations Trial (DCCT) for an average of 35 years, showed that only 1.2% had a stimulated C-peptide level of at least 0.2 pmol/mL. An additional 100 patients (10.5%) had some detectable C-peptide response. Any detectable C-peptide response (i.e., >0.03 pmol/mL) is of clinical value. In the EDIC study, detectable C-peptide was associated with a reduced risk of severe hypoglycemia (adjusted odds ratio = 0.35, $P < 0.0001$) (Gubitosi-Klug et al. 2021). Similar rates of progression and protection from severe hypoglycemia were seen in the Scottish Diabetes Research Network Type 1 Bioresource (SDRNT1BIO) cohort of 6076 people with T1D (Jeyam et al. 2021).

There is little evidence of sustained spontaneous recovery of β cells after the diagnosis with stage 3 T1D. Within weeks after clinical presentation, there may be a transient improvement in β -cell function (i.e., the “honeymoon”) but the decline in function then continues in a near-linear manner following a pattern that was established before the clinical diagnosis. With modeling studies, these parameters have been used to predict the loss of C-peptide with time in any individual patient. This quantitative response (QR) can be used to identify early signs of effective therapies and with fewer subjects than with standardized randomized placebo-controlled trials (Bundy et al. 2020; Ylescupidiez et al. 2023; Pribitzer et al. 2024). In patients treated with immune therapies, the magnitude of the improvement during the honeymoon is exaggerated but in most cases, a decline follows. At later times after the diagnosis, the improvement in β -cell function is rarely seen although a report of treatment of patients age 25 and ~ 1 year after clinical diagnosis with T1D with ATG did show improvement in stimulated C-peptide levels. At 6 months after ATG treatment, there was an 11.3% improvement in the area under the curve (AUC) (Haller et al. 2015).

IMPLICATIONS OF STUDIES ON DISEASE INITIATION AND PROGRESSION FOR CLINICAL STUDIES—STILL MORE WORK TO BE DONE

The recognition that T1D is a progressive disease in which the ongoing process can be identified

has opened up the opportunity to intervene before and even after the diagnosis (these studies are described in Tatovic and Dayan 2024). The investigations of disease mechanisms suggest appropriate targets for therapies, but also have identified features that have not been addressed and require consideration for the design of future clinical studies. First, the effects of age and variability even with age adjustment complicate the design of prevention studies and require sample sizes that are larger than those needed to evaluate drug treatment effects in patients with new-onset T1D. For example, in the recently completed trial of abatacept in patients with $\geq 2+$ autoantibodies but without glucose intolerance (i.e., stage 1 T1D, see below) (TN18), the median time to progression to glucose intolerance in the placebo treatment arm ($n = 111$) was 71.5 months but in those that progressed ($n = 45$) the time until glucose intolerance varied widely (range 5.3–100.5 months) (Russell et al. 2023). Even in those who have $>2+$ autoantibodies and glucose intolerance, the median time to diagnosis with clinical T1D is 27.7 months ($n = 32$) and in those who do progress ($n = 28$), the time varied (range 2.4–85.5 months) (Sims et al. 2021).

Second, by the time that these serologic markers can be identified in the peripheral blood, antigen presentation, and activation of immune cells have been established. Arresting an ongoing activated immune response is more challenging than primary prevention, and it requires intervention in young individuals. Genetic screening alone cannot determine the timing of the initiation of autoimmunity. Therefore, agents to be considered before stage 1 disease need to be safe with extended efficacy.

Third, the finding of endotypes may reflect different disease mechanisms or other features that require a personalized approach to therapies. The TEDDY study has shown that individuals presenting with IAA show an expansion of NK cells, which is not found in those who present with GADA as their first-appearing autoantibody (Krischer et al. 2019). In addition, the B-cell infiltrates that are found more in children than adults and the differences in immunologic markers between endotypes even raise the possibility of a different pathogenic mechanism

(Smith et al. 2020). Therefore, not all therapies are likely to be effective in all patients. Identifying the clinical and mechanistic differences among these endotypes is ongoing and may be aided by the analysis of the responses of individuals to immune perturbations by therapies. These investigations may improve the matching of specific agents for individual patients.

Fourth, we do not have a way of measuring the active autoimmune process directly in islets, and, therefore, to date, endpoints have required clinical outcomes that require extended follow-up. As discussed above, autoantibodies are markers of immune priming but themselves do not destroy β cells. Several groups have developed methods for the analysis of antigen-specific T cells and have postulated that these cells can mediate β -cell killing. The effectiveness of anti-T-cell drugs such as teplizumab and ATG supports this contention. The absence of a direct measure of disease activity has practical consequences since T-cell and even other therapies have been shown to be most effective when the disease process is active. If there is reactivation of autoreactive cells, combinations of or even repeated therapies will be needed.

CONCLUSIONS

Data from multiple disciplines over the past four decades that includes preclinical studies in murine models analysis of human samples from blood and from the pancreas at the time of death and results from clinical studies have established T1D as an autoimmune disease leading to metabolic failure of β cells. Genetic studies have identified high risk and other genes that are linked to the disease but the factors that initiate disease in those at genetic risk remain uncertain. The reduced exposure to viral and bacterial infections and improvement in living conditions, particularly among developed countries, are consistent with the central tenet of the “hygiene hypothesis,” which suggests that exposure to environmental pathogens may lead to reduced autoimmunity. The chronicity of β -cell killing and multiple targets of the autoimmune response that evolve over time suggest there is a dynamic process between the target (β) and immune cells.

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Biologic markers of patients at risk can identify T1D before clinical presentation. The combination of metabolic and immune testing can determine risk, but the actual rate of disease progression and the pathologic activity is not directly measured. Nonetheless, these tools have enabled the approval of the first successful treatment to delay T1D onset in patients at risk with teplizumab.

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