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Type 1 Diabetes Prevention: Screening Efforts and Prevention Studies in At-Risk Relatives and the General Population

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ABSTRACT

Type 1 diabetes autoantibodies are detectable before the onset of clinical disease. Once an individual has ≥2 diabetes autoantibodies, their lifetime risk of developing clinical disease approaches 100%. While relatives of individuals with type 1 diabetes have a 15-fold increase in disease risk, 85-95% of type 1 diabetes diagnoses occur in people without affected relatives. Identification of multiple diabetes autoantibodies and subsequent education and monitoring prior to clinical type 1 diabetes diagnosis decreases the incidence of diabetic ketoacidosis at onset as well as other diabetes sequelae. Also, early risk recognition facilitates participation in clinical trials aimed at delay and prevention of clinical disease and/or treatment with teplizumab, an approved medication to delay onset of clinical type 1 diabetes in people with multiple diabetes autoantibodies and dysglycemia. Therefore, risk screening, which is currently recommended only for relatives of individuals with type 1 diabetes, should be expanded to include the general population.

Introduction

Type 1 diabetes (T1D) affects approximately 1 out of every 300 children in the United States.[1] Individuals with a family history of T1D have the highest risk of developing the disease. Having a first-degree relative (parent, sibling, or child) with T1D confers a 15-fold increase in T1D risk[2]. Despite the increased risk of T1D among family members, T1D is not familial in most cases. Estimates show that of those who develop T1D, only 5 to 15% have a positive family history.[2,3]

Studies of T1D relatives who developed clinical disease have enabled researchers to characterize the pathogenesis of T1D, allowing accurate prediction of the rate of progression. Autoantibodies to insulin (insulin [IAA]), islet cells (islet cell antigen [ICA512] and insulinoma-associated protein 2 [IA-2]), and/or related islet cell proteins (glutamic acid decarboxylase [GAD] and zinc transporter 8 [ZnT8]) appear prior to clinical disease. An individual has stage 1 T1D when they have ≥2 T1D autoantibodies and normoglycemia. At this point, their five-year risk for progressing to clinical T1D is 44%, ten-year risk is 70%, and lifetime risk approaches 100%. When a person has ≥2 autoantibodies and dysglycemia (fasting glucose 110-125 mg/dL and/or 2-hour post-prandial glucose between 141 and 199 mg/dL and/or glucose >200 mg/dL during an oral glucose tolerance test), they have stage 2 T1D. Their five-year risk for progression to clinical T1D is 75% and their lifetime risk approaches 100%. Stage 3 T1D is clinical T1D as defined by the American Diabetes Association (ADA). General population studies have demonstrated that once an individual has ≥2 T1D autoantibodies, the risk for progression to clinical T1D is the same regardless of whether the person has an affected relative.[4,5]

There are multiple benefits to diagnosing T1D during stages 1 and 2. Identifying pre-clinical (pre-symptomatic) T1D provides the opportunity for careful monitoring to decrease the rate and severity of diabetic ketoacidosis (DKA) at the onset of clinical T1D. DKA, a potentially life-threatening condition, is common at presentation of clinical T1D and is often unrecognized until a person is critically ill.[6] Individuals with DKA are at risk for acute cerebral edema as well as neurocognitive damage. Diabetic ketoacidosis at T1D diagnosis has also been associated with successive episodes of DKA as well as subsequent severe hypoglycemia and worse glycemic control, which is known to increase the risk of both microvascular and macrovascular T1D complications.[7] Rate of DKA at T1D diagnosis ranges from 15 to 80% globally. However, identification of T1D during the presymptomatic stages (stages 1 and 2) with consequent monitoring can drop the rate of DKA at clinical T1D onset to <5%.[7] In addition to decreasing the incidence of DKA at diagnosis, early identification of individuals at risk for the development of stage 3 (clinical) T1D can provide patients and families with time to adjust to the diagnosis and become educated about the disease and its management. Another benefit of identifying T1D at stages 1 and 2 is the opportunity for possible participation in clinical research studies aimed at delay and/or prevention of progression to clinical (stage 3) disease. Also, stage 2 individuals can be eligible for treatment with teplizumab, a humanized anti-CD3 monoclonal antibody approved by the U.S. Food and Drug Administration in November 2022 for the delay of onset of stage 3 T1D in people with stage 2 disease.[8]

Numerous clinical trials aimed at delaying and/or preventing progression from stage 1 and stage 2 T1D to stage 3 disease have been conducted. Only teplizumab demonstrated benefit in the delay of advance to clinical disease. To date, prevention studies have identified nearly all participants by screening relatives of individuals with T1D for diabetes autoantibodies and glycemic status. While some researchers have conducted T1D screening studies in the general population, very few clinical trials have focused on prevention in those determined to have stage 1 and stage 2 T1D. In 2017, the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommended T1D autoantibody screening in the setting of a research study as well as in first-degree family members of people with T1D. In 2022, ISPAD acknowledged the value of general population screening as well as the importance of associated education and monitoring of those found to be at risk. Following the approval of teplizumab for delay of clinical T1D onset in stage 2 disease, the World Health Organization (WHO) acknowledged that the criteria for screening the general population for T1D had been satisfied.[7]

Type 1 diabetes screening is currently recommended for first-degree relatives of individuals with T1D. However, general population screening is rarely performed outside of a research setting despite the well-established benefits of identifying pre-clinical T1D and the fact that the overwhelming majority of new T1D cases occur in individuals without affected relatives. This manuscript provides a description of screening efforts in both T1D relatives and non-relatives (general population) as well as primary and secondary prevention studies performed to date in support of screening and monitoring both T1D relatives and the general population.

Précises of Screening and Prevention Studies

SCREENING STUDIES

A. T1D Relatives

Bart's Oxford Family Study

In Oxford, England, investigators conducting the Bart's Oxford (BOX) Family Study evaluated 1,430 siblings and 2,419 parents of children with T1D to examine the relationship between proband age of T1D onset and familial risk. They found that 53 siblings (3.7%) and 106 parents (4.4%) developed T1D during the follow-up period. Affected siblings progressed to T1D by a median age of 16.5 years, and parents developed clinical T1D by 44 years of age. Early onset of T1D in the proband (<5 years of age) was a powerful risk modifier for T1D in siblings and parents. Specifically, when the proband was diagnosed by the age of 5 years, siblings had a T1D cumulative incidence of 11.7% by age 20 compared to 3.6% and 2.3% when the proband was diagnosed at ages 5-9 and 10-14 years of age respectively. Similarly, when the proband was diagnosed by the age of 5 years, parents had a cumulative incidence of 5.9% by age 40

compared to 3.7% when the proband was diagnosed at older ages. Among 1,169 unaffected siblings, when the proband was <5 years of age at T1D diagnosis, 7.3% developed ≥2 T1D autoantibodies during the study follow-up period, which was much higher than the 2.2-2.4% observed when clinical T1D onset in the proband occurred at an older age. The overall T1D autoantibody positivity rate among relatives of individuals with T1D in the BOX study was 7%. The BOX Family Study investigators concluded that early onset T1D in the proband is a very strong marker of increased familial risk for both T1D autoimmunity and clinical disease in first-degree relatives.[9]

TrialNet Pathway to Prevention Study

TrialNet was established in 2001 as an international clinical research consortium focusing on the development and implementation of studies aimed at the delay and prevention of T1D. To identify and recruit eligible individuals for these studies, TrialNet launched its Pathway to Prevention Study. The Pathway to Prevention Study has screened >180,000 relatives of people with T1D and recruited >15,000 at-risk individuals into TrialNet monitoring and intervention studies.[10]

Information gained from TrialNet's monitoring of at-risk individuals significantly contributed to the definition of T1D stages based on T1D autoantibody presence and glucose tolerance. TrialNet has identified many at-risk and new-onset relatives (stages 1, 2, and 3) for enrollment into TrialNet prevention and new-onset trials. TrialNet's T1D autoantibody positivity rate among family members is 5.5%.[11]

INNODIA

INNODIA, launched in 2016, is a European consortium of researchers focused on better predicting, staging, evaluating, and preventing the onset and progression of T1D. The INNODIA study is divided into two arms. The first recruited 1,500 individuals within 6 weeks of T1D diagnosis for monitoring over 2 years. These T1D participants have provided information about T1D heterogeneity as well as a pipeline for recruitment into new-onset studies.[12] The second arm is screening 4,500 unaffected first-degree family members of individuals with T1D for monitoring of T1D autoantibodies over 3 years. INNODIA's T1D autoantibody positivity rate among family members is 6%. Family members who do not have T1D and are autoantibody positive are being monitored regularly for ~4 years. Outcomes from the second arm are pending.[13]

Type1Screen

Type1Screen, a prospective nationwide screening initiative in Australia, aimed to identify T1D autoimmunity among individuals who had a family history of T1D to allow early intervention to delay or prevent progression to clinical T1D and to avoid DKA at T1D diagnosis. Over a two year period, relatives of individuals with T1D were screened by capillary blood spot (n=967) or venipuncture (n=276) for T1D autoantibodies. Of those screened, the overall T1D autoantibody positivity rate was 5.9%. By the end of the two year period, 12 participants had progressed to clinical (stage 3) T1D, and none presented with DKA, confirming the importance of early detection. Type1Screen investigators concluded that in-home screening in this population was feasible and effective and could be used more broadly in at-risk populations to enable timely diagnosis without the burden of DKA as well as enrollment into disease-modifying trials.[14]

B. General Population

Global Platform for the Prevention of Autoimmune Diabetes

Global Platform for the Prevention of Autoimmune Diabetes (GPPAD), launched in 2015, was designed to identify infants with high genetic risk for T1D so that they could be enrolled in primary prevention trials. A total of 50,669 infants were screened at birth or at routine health visits before the age of 5 months across five European countries, including 891 infants (1.76%) with a T1D-affected first-degree relative. Determination of genetic risk for development of multiple T1D autoantibodies prior to age 6 years was determined by a newly developed risk score based on 46 T1D susceptibility single-nucleotide polymorphisms (SNPs) or 3 SNPs plus a first degree relative with T1D. Of the infants screened, 1.1% with high T1D genetic risk (>10%) were identified, followed, and offered participation in a randomized, controlled trial aimed at the prevention of T1D autoimmunity and clinical T1D by the induction of tolerance with oral insulin.[15] This trial, the GPPAD-POInT study, is described in the primary prevention section below.[16]

Diabetes Prediction and Prevention Study

The Finnish Diabetes Prediction and Prevention (DIPP) Study, initiated in 1994, provided insight into genetic and familial contributions to T1D autoimmunity and progression to T1D. In a 2020 publication by Kuusela et al, researchers evaluated children's T1D genetic risk to determine the impact of positive family history on their progression to T1D autoimmunity and clinical T1D. A total of 343 children who were positive for at least 1 T1D autoantibody were analyzed, and of these, 45 progressed to T1D. Of the 45, 28 (62.2%) had at least one relative with T1D, and in 26 of the 28, it was a second- rather than first-degree relative. This data supports the conclusion that having a relative with T1D in the family, whether it is first- or second-degree, is a significant risk factor for the development of T1D autoantibodies and clinical T1D. This study also demonstrated a significant association between having a higher number of autoantibodies (2-4) and the likelihood of having a T1D family history. Maternal T1D was associated with an earlier age of seroconversion in children, but for children with multiple T1D autoantibodies, age at seroconversion was not affected by family history, suggesting that genetic and/or environmental factors related to maternal T1D might affect the initial development of T1D autoimmunity but not its subsequent trajectory.[17]

BABYSCREEN

BABYSCREEN is a research study focused on progression to T1D and celiac disease in genetically at-risk newborns. The study sought to identify children with a hereditary predisposition for T1D at birth to reduce issues associated with progression to T1D clinical diagnosis. Participants

were recruited from two hospitals in Finland between 2018 and 2021. Umbilical cord blood was screened after birth for high risk Human Leukocyte Antigen (HLA) genotypes. Infants found to be at increased risk during screening were monitored until the age of 3 years for the development of T1D and celiac autoantibodies as well as clinical disease. Follow-up was completed in 2024. A total of 9,779 newborns were screened for genetic factors predisposing to T1D and celiac disease. Of these, 6.0% had a hereditary predisposition to T1D, 14.8% to celiac disease, and 4.0% to both T1D and celiac. Of the 9,779 newborns, 2,430 were determined to be eligible for enrollment due to an at-risk genotype, and 1,827 (75%) agreed to participate in follow-up. Analysis of the collected samples/data is underway, and initial results are expected to be published in 2025.[18]

Combined Antibody Screening for Celiac and Diabetes Evaluation

Combined Antibody Screening for Celiac and Diabetes Evaluation (CASCADE), launched in 2020, is a research study aimed at screening for T1D and celiac risk in children living in Washington state. Once children are enrolled, leftover blood samples from state newborn screening are used to look for markers of T1D and celiac risk. Children found to be at risk are offered enrollment into a follow-up monitoring study.[19]

Population Level Estimation of Type 1 Diabetes Risk Genes in Children

The Population Level Estimation of Type 1 Diabetes Risk Genes in Children (PLEDGE) study, started in 2020, is performing general population T1D autoantibody screening. A targeted SNP-based genetic risk score is performed at study entry (as early as during the newborn period), and T1D autoantibodies are collected at routine clinic appointments at about 2 and 5 years of age, or once between 9 and 16 years of age. Children with positive autoantibodies are offered monitoring and the opportunity to be considered for a TrialNet clinical trial. As of late 2024, >70 autoantibody positive children had been identified as at-risk for T1D. Five progressed to stage 3 (clinical) T1D, and none had DKA or significant symptoms at diagnosis.[20,21]

Fr1dolin

Fr1dolin was a population-based T1D screening initiative conducted in Germany to identify asymptomatic children with T1D autoimmunity and provide early-stage diagnoses prior to the onset of clinical disease. During the early part of the study (2015-2019), 90,632 children aged 2 to 5 years were screened for T1D autoantibodies during routine pediatric visits. Of these, 280 (0.31%) were found to have presymptomatic T1D (196 stage 1, 17 stage 2, 26 stage 3, and 41 unstaged). During a median follow-up of 2.4 years, an additional 25 children progressed to stage 2 and 36 progressed to stage 3, illustrating the progressive nature of the disease. The investigators pointed out that among children between 2 and 5 years of age, primary care-based screening demonstrated a T1D autoantibody prevalence of 0.31%, which may inform consideration of population-based screening for T1D autoantibodies.[22]

Fr1da

The Fr1da study, a population-based T1D screening initiative that began in 2015 in Germany, targeted the identification of asymptomatic children with islet autoimmunity to provide early-stage diagnoses prior to the onset of stage 3 (clinical) disease. This study screened 169,446 children without known T1D during routine pediatric visits, aged 1.75 to 10.99 years, for T1D autoantibodies. Stages 1 and 2 (asymptomatic, preclinical) T1D were diagnosed when multiple autoantibodies were positive. Children with presymptomatic T1D were offered metabolic staging, information on recognition of hyperglycemia and DKA symptoms, and monitoring. Families that declined staging/monitoring were contacted to determine the timing of stage 3 T1D onset. At clinical T1D diagnosis, children with prior early-stage diagnosis had significantly lower median glycated hemoglobin (HbA1c), lower median fasting glucose, higher median fasting C-peptide, lower ketonuria, and lower insulin requirement compared to children without early-stage diagnosis. In addition, only 2.5% of those with prior early-stage diagnosis presented with DKA at diagnosis, and clinical presentation was milder in those who participated in education and monitoring after early-stage diagnosis. There was no association between prior early stage diagnosis and family history of T1D. Investigators concluded that diagnosis of presymptomatic T1D followed by education and monitoring resulted in better clinical presentation at T1D clinical onset.[23]

T1Detect

T1Detect is an online resource for the early screening, detection and treatment of T1D. This program offers at-home T1D autoantibody screening to facilitate detection of pre-symptomatic T1D in both relatives of people with T1D and individuals without a family history of T1D. Using a dried blood spot collection kit, participants are tested for T1D autoantibodies. Among the first 800 participants (approximately 74% with a positive family history), 96 individuals (12%) were positive for a single autoantibody, 32 (4%) had 2 autoantibodies, and 13 (1.63%) had 3. The program also provides structured online and phone-based follow-up support for individuals testing positive, integrating clinical guidance into post-screening care. The T1Detect model demonstrates that at-home, mailed screening kits for the detection of T1D autoantibodies is feasible and scalable, achieving autoantibody detection rates comparable to clinical screening programs while expanding access.[2,5]

Precision Individualized Medicine for Diabetes

In 2021, University of Virginia launched the Precision Individualized Medicine for Diabetes (PrIMeD) project in 8 pediatric clinics within the Commonwealth of Virginia. Investigators obtained saliva samples on 3,818 children, aged 2 to 16 years, with or without a family history of T1D. Genetic risk score (GRS) testing on DNA extracted from the saliva incorporated both HLA and non-HLA variants. Those found to be at high genetic risk, 542 children (14.2%), were offered screening for T1D autoantibodies. Of the 494 who had high genetic risk and no pre-existing T1D, 28 (5.7%) consented to and followed through with screening. Two of the 28 (7.1%)

tested positive for multiple T1D autoantibodies. Among the 91 children with pre-existing T1D, 48 (52%) had high genetic risk. There was no relationship between genetic risk and age of T1D onset. A follow-up survey, completed by 2,096 (55%) participants at least one year post-enrollment, identified 2 new cases (0.095%) of T1D. The low rate of uptake on autoantibody testing was thought to be limited by the SARS-CoV-2 pandemic and concerns for infectious exposure at sample collection. Study investigators concluded that minimally invasive saliva sampling to determine a T1D genetic risk score is feasible and can identify children with genetic risk for T1D.[24]

Autoimmunity Screening for Kids

In 2017, the Barbara Davis Center in Denver, Colorado launched the Autoimmunity Screening for Kids (ASK) program, a large, presymptomatic T1D screening program for children. The goal was to assess and project cost-effectiveness of screening compared to standard of care (no screening). During the initial phase of the study (18 months), 10,029 children were evaluated, and only 5% of these had a first-degree relative with T1D. Among those screened, 3.1% tested positive for ≥1 T1D autoantibody, while 0.58% had confirmed multiple T1D autoantibodies, placing them at approximately 70% risk of developing T1D within 10 years. Analyses demonstrated a screening cost of ~$47 per child versus $141 for routine screening outside of the study and ~$4,700 per case detected under the research protocol versus $14,000 when done by routine screening. A clinical outcomes analysis showed that participants with multiple T1D autoantibodies had dramatically reduced DKA rates at diagnosis (<5%) compared to 62% in outside cases. In addition, they demonstrated better glycemic control (average HbA1c 7.3% versus 11.9%) and lower severe DKA incidence (1.2% versus 16.2%). Preliminary data from this study showed that general population screening is both feasible and cost-effective. The ASK model illustrates a scalable approach to early T1D autoimmunity detection and offers a template for future public health implementation.[25]

T1Early

T1Early is a general population screening program in the United Kingdom. Investigators are measuring T1D autoantibodies by capillary blood sample in preschoolers during a vaccination visit to their primary care physicians (at age 3.5 to 4 years). A creative design agency is being used to inform the public, raise awareness about preclinical diabetes, and embed T1D screening within the health system.[5]

Screening for Islet Autoantibodies in the Israeli Pediatric General Population for Detection of Presymptomatic Type 1 Diabetes

Screening for Islet Autoantibodies in the Israeli Pediatric General Population for Detection of Presymptomatic Type 1 Diabetes (ADIR), started in Israel in 2021, coordinates capillary blood T1D autoantibody screening with scheduled primary care physician hemoglobin screening at 9-18 months and 5 years. The ADIR study plans to screen approximately 50,000 children.[5]

Juvenile Diabetes Research Foundation Australia General Population Screening Pilot

The Juvenile Diabetes Research Foundation (JDRF) Australia General Population Screening Pilot is planning to screen newborns, infants, and 2- to 6-year-olds for genetic risk as well as T1D autoantibodies. They will test capillary blood and saliva samples to compare genetic risk to T1D autoantibody screening in older children.[5]

PREVENTION STUDIES

A. Primary Prevention Studies

Vitamin D and Omega-3 Fatty Acid

Studies demonstrated that cod liver oil taken by mothers during pregnancy or by infants during the first year of life was associated with a decreased risk of T1D development. It was unclear, however, which component(s) of the cod liver oil (vitamin D, eicosapentaenoic acid [EPA], and/or docosahexaenoic acid [DHA]) were responsible for the protective effects.[26,27] In addition, epidemiologic, immunologic, and mouse studies have suggested that Vitamin D administration could achieve T1D primary prevention.[28-30]

In 2006, Wicklow and Tabak published preliminary data from a study evaluating the feasibility of identifying, recruiting, and randomizing babies with T1D genetic HLA risk into a prevention trial comparing the daily administration of 400 to 2,000 IU of vitamin D3 by mouth over 12 months (starting by 1 month of age). Of the 669 mothers approached, 67% consented to participate, and after HLA testing, 7 genetically at-risk babies were enrolled and randomized. Measurements of auxology, bone density, serum markers (calcium, phosphate, creatinine, 25-hydroxyvitamin D, 1,25-hydroxyvitamin D), and urine markers (calcium, phosphate, creatinine) as well as renal ultrasound were performed. All results were unremarkable, suggesting that 2,000 IU of vitamin D3 was safe and acceptable to families of infants with increased genetic risk.[31]

In 2015, Chase et al published results of a multi-center, two-arm, double blind, randomized pilot trial comparing the effect of DHA supplementation to placebo on inflammatory cytokine production. Babies were enrolled during the last trimester of pregnancy (n=41) or the first 5 months after birth (n=57). All participating infants were required to have a first-degree relative with T1D and had to be genetically at risk for T1D (positive HLA DR3 or DR4) and/or had to have multiple first degree relatives with T1D. For those enrolled while their mothers were pregnant, DHA supplements were discontinued at birth if the baby was not found to be genetically at risk (HLA DR3 and/or DR4 positive) and did not have multiple relatives with T1D. Infants enrolled during the first 5 months of life were required to be positive for HLA DR3 and/or DR4 and/or to have multiple first degree relatives with T1D. This study demonstrated a 61-100% increase in red blood cell (RBC) DHA in those who received supplementation and established the safety of this intervention but failed to show a consistent reduction in inflammatory cytokine production.[32]

Oral Insulin

In 1991, Zhang et al demonstrated that oral administration of porcine insulin to nonobese diabetic mice affected the pancreatic cellular inflammatory process and the development of T1D, raising the possibility that this approach could be used to delay and/or prevent T1D in humans.[33] The Primary Oral Insulin Trial (Pre-POInT), GPPAD-POInT, and Pre-POInT-early (Primary Oral Insulin Trial-Early) evaluated the effect of oral insulin on the development of T1D autoantibodies in at-risk individuals.

Results generated by the Pre-POInT pilot trial were published in 2015 by Bonifacio et al. This study, conducted in Germany, Austria, the United States, and the United Kingdom between 2009 and 2013, enrolled T1D autoantibody negative children who were 2 to 7 years of age and at high risk for the development of T1D (≥2 first degree relatives with T1D and a high risk HLA haplotype and/or a sibling with T1D and a high risk HLA genotype identical to the sibling with T1D). This randomized, placebo-controlled, double-blind, dose-escalation trial evaluated immune response to insulin compared to placebo. For 3 to 18 months, 15 children were treated with daily oral insulin (2.5 to 7.5 mg [n=3], 2.5 to 22.5 mg [n=3], 7.5 to 67.5 mg [n=3], 22.5 mg throughout [n=3], and 67.5 mg throughout [n=3]) and 10 were treated with placebo. Only those who received 67.5 mg of oral insulin daily developed an immune response, and hypoglycemia was not observed. The investigators concluded that their findings supported the need for a larger trial to evaluate whether oral insulin can be used to prevent T1D autoimmunity and clinical T1D in at-risk children.[34]

In 2019, Ziegler et al published an update on the GPPAD-POInT study. This trial, being performed in Germany, Poland, Belgium, United Kingdom, and Sweden, is enrolling infants aged 4 to 7 months with a >10% risk for the development of multiple T1D autoantibodies as determined by genetic risk score or family history combined with HLA genotype. Participating infants are randomized to receive either oral insulin, 67.5 mg daily (at the end of a 4 month dose escalation), or placebo for 3 years. Participants will be followed for up to 7 years. Primary outcome is confirmed development of multiple T1D autoantibodies. This study is currently underway.[35]

In 2021, Assfalg et al published findings from the Pre-POInT-early study, conducted at a single site in Germany. This trial was designed to assess the safety and efficacy (immune response and gut microbiome immunity) of oral insulin administration. Forty-four children, aged 6 months to 3 years, who were negative for T1D autoantibodies and had a first-degree relative with T1D and a high-risk HLA genotype, were randomized to receive either oral insulin (7.5 mg escalating to 67.5 mg) or placebo for 12 months. Primary outcome was T1D autoantibody development and/or T cell response to insulin. Oral insulin was well tolerated and no safety signals were identified during the study. The trial did not show any effect on the primary outcome variables. Exploratory analyses suggested that T1D autoantibody responses to oral insulin children may be seen in children with a susceptible insulin gene (INS) genotype and that inflammatory episodes may encourage activation of T cells that are responsive to insulin.[36]

Intranasal Insulin

Primary Intranasal Insulin Trial (PINIT) investigators hypothesized that administering intranasal (mucosal) insulin to children genetically predisposed to T1D might induce pancreatic β-cell immune tolerance to protect against islet autoimmunity and T1D. PINIT, launched in 2018 by Achenbach et al, was a double-blind placebo-controlled trial of intranasal insulin in Germany. The study enrolled 38 children, ages 1 to 7 years, who were negative for T1D autoantibodies and had a high-risk HLA haplotype and/or no protective HLA alleles or haplotypes. Intranasal insulin (440 IU) or placebo was administered once daily for 7 days and then once each week for 6 months. In 2022, the investigators reported that no difference was observed in the primary outcome, immune efficacy as measured by activation of an immune response to insulin (T1D autoantibodies or CD4 T cells), between treatment groups. There were no serious adverse events in the active treatment group, and the intranasal insulin was well tolerated.[37]

Delayed Cow's Milk (Bovine) Insulin Exposure

Short duration of breast-feeding and earlier exposure to more complex dietary proteins has been implicated in the development of β-cell autoimmunity and T1D.[38]

Vaarala et al conducted the Finnish Dietary Intervention Trial for the Prevention of Type 1 Diabetes (FINDIA) pilot study to evaluate whether weaning to a cow's milk formula free of bovine insulin reduced the risk for T1D autoantibody development in children with genetic risk. Three hospitals in Finland recruited 1,113 infants with T1D HLA susceptibility to a randomized study comparing whey-based formula to whey-based formula free of bovine insulin (when breast milk was not available) during the first 6 months of life. Primary outcome was β-cell autoimmunity at 3 months, 6 months, 1 year, 2 years, and 3 years. Results, reported in 2012, demonstrated that children at genetic risk of T1D who received insulin-free cow's milk (FINDIA) formula had a reduced incidence of T1D autoantibodies by 3 years of age.[39]

Results from the Trial to Reduce Insulin-Dependent Diabetes Mellitus in the Genetically at Risk (TRIGR) were reported in 2018 by Knip et al. This international double-blind, placebo-controlled clinical trial randomized 2,159 infants with T1D HLA susceptibility and a first-degree relative with T1D to receive, once weaned, either an extensively hydrolyzed casein-based formula or a formula made up of 80% intact cow's milk protein and 20% hydrolyzed milk protein. The dietary intervention was continued until the infant was 6 months old, and if they had not received at least 60 days of the study formula, it was continued until 60 days of study formula was received or 8 months of age was reached. Primary endpoint, T1D diagnosis, by a median of 11.5 years of follow-up, revealed that weaning to a hydrolyzed formula did not decrease the cumulative incidence of T1D.[40]

Delayed Gluten Exposure

Prospective studies in humans have demonstrated that the introduction of solid foods (including those with gluten) affects the development of T1D autoantibodies in children with genetic susceptibility to T1D. Two studies have shown an increase in T1D autoantibodies in children exposed to gluten prior to 4 months of age and one study also demonstrated increased risk when gluten exposure was delayed beyond 6 months of age.[41,42] A study in T1D autoantibody-positive children showed that β-cell function may be improved when gluten is not introduced during the first 6 months of life.[43] The BABYDIET study, conducted in Germany, was aimed at determining whether delay in the introduction of gluten in genetically at-risk infants may reduce T1D-associated autoimmunity. The trial randomized 150 infants with a T1D high-risk HLA genotype and a first-degree family member with T1D to receive either first gluten exposure at 6 months of age (control group) or 12 months of age (late-exposure group). Participants were followed every 3 months until 3 years of age for autoantibody development and T1D. Study results, published in 2011, failed to demonstrate a reduction in T1D autoantibody development and T1D when gluten exposure was delayed to 12 months.[44]

Bifidobacterium infantis

Studies have demonstrated that early probiotic supplements may decrease T1D autoantibody development in children at high genetic risk for T1D.[45] The GPPAD-SINT1A study is aimed at determining whether early daily *Bifidobacterium infantis* administration will reduce the incidence of β-cell autoantibodies in children with a high T1D risk score or a family history of T1D in addition to a high risk HLA genotype. Infants between 7 days and 6 weeks of age are being randomized to receive either *Bifidobacterium infantis* or placebo until 12 months of age. Primary outcome, development of persistent, confirmed T1D autoantibodies, will be assessed no more than 5.5 years after completing treatment. The study completed enrollment (n=1,149) and is expected to reach its primary endpoint in late 2027.[46]

B. Secondary Prevention Studies

Nicotinamide

Studies published in 1982 and 1993 demonstrated that high doses of the nicotinamide (a B vitamin) delayed or prevented diabetes development in non-obese diabetic (NOD) mice, a model of human T1D.[47,48]

In 1998, Lampeter et al published results of the Deutsche Nicotinamide Intervention Study (DENIS). In this trial, 55 children (ages 3 to 12 years) with elevated ICA titers were randomized to a double-blind, placebo-controlled trial comparing sustained release nicotinamide to placebo. Nicotinamide dose was 1.2 g/m^2 (body surface area) divided into twice daily doses for a maximum of 5 years. The primary outcome was development of T1D. The Deutsche Nicotinamide Intervention Study was terminated when interim analysis following the eleventh case of T1D demonstrated futility due to no reduction in T1D incidence. This study could not exclude the possibility of a less strong but possibly meaningful risk reduction.[49]

Results from the European Nicotinamide Diabetes Intervention Trial (ENDIT), a similar study to DENIS, were published in 2004. This randomized, double-blind, placebo-controlled trial enrolled 552 relatives of individuals with T1D who had elevated levels of ICA and non-diabetic oral glucose tolerance tests. Participants were randomized to receive either oral modified release nicotinamide, 1.2 g/m^2 (body surface area), or placebo for 5 years. Primary outcome was the development of T1D. The European Nicotinamide Diabetes Intervention Trial failed to demonstrate any difference in progression to T1D between the treatment and control groups.[50]

Parenteral Insulin

Early pilot studies of parenteral insulin administration in humans suggested that this intervention can delay or prevent progression to T1D in at-risk individuals.[51-53]

The Diabetes Prevention Trial – Type 1 (DPT-1) was a randomized, controlled, non-blinded study of parenteral insulin administration in 339 first- (ages 3 to 45 years) and second-degree (ages 3 to 20 years) relatives of individuals with T1D who had a high (>50%) 5-year risk of developing clinical T1D. Risk level was defined as having positive ICA, abnormal first-phase insulin response (FPIR) on intravenous glucose tolerance test, dysglycemia on oral glucose tolerance test, and no protective HLA haplotype. Those with high risk were randomized to either an untreated control group that was closely observed or to subcutaneous insulin injections (recombinant human [rh] ultralente), 0.125 units/kg body weight twice daily as well as an annual continuous intravenous infusion of regular insulin lasting 4 days (0.015 units/kg body weight) with increase during meals to keep blood glucose at 60-80 mg/dL. Primary outcome was progression to clinical T1D. In 2002, the DPT-1 study group reported that the trial failed to demonstrate a benefit of parenteral insulin administration with respect to the delay or prevention of T1D.[54]

In 2002, following publication of the DPT-1 parenteral insulin study results, Carel et al reported the results of a similar, albeit smaller, trial. This study enrolled 29 children, relatives of T1D patients and T1D autoantibody positive individuals, into the European Prediabetes Prevention – Subcutaneous Insulin Trial (EPPSCIT). This randomized, double-blind trial involved the administration of either ultralente insulin (0.2 U/kg before breakfast) or placebo for a median of 3 years. Primary outcome was the development of T1D. The incidence of progression to T1D was similar in the treatment and control groups and to that observed in DPT-1.[55]

The Belgian Diabetes Registry study group reported the results of a parenteral insulin trial in IA-2-positive relatives of individuals with T1D in 2009. Participants were treated with either regular human insulin (n=12) or placebo (n=15) for between 27 and 67 months. Insulin treatment was well tolerated but the primary outcome, progression to clinical T1D, did not differ between the two treatment groups.[56]

Oral Insulin

In the 1990s, oral administration of insulin to pre-diabetic NOD mice was shown to inhibit the development of T1D, leading to several studies assessing the feasibility and efficacy of this approach to T1D prevention in humans.[54,57-62]

The DPT-1 oral insulin study was a randomized, double-blind, placebo-controlled trial to determine whether oral insulin administration could delay or prevent disease progression in first- and second- degree relatives of people with T1D. Randomization of 372 (median age 10.25 years) individuals with a 26-50% 5-year risk of advance to clinical T1D to either oral insulin (7.5 mg/day) or placebo occurred at study start, and oral glucose tolerance tests were done every 6 months. Mean follow-up was 4.3 years, and primary endpoint was T1D diagnosis. Annualized rate of progression to T1D was comparable in both groups, suggesting that oral insulin did not delay or prevent T1D. Post hoc analysis of a subgroup with confirmed IAA levels ≥80 nU/mL (n=263) showed a possible benefit of oral insulin (p=0.015).[54]

TrialNet enrolled 561 relatives of individuals with T1D who had ≥2 T1D autoantibodies, normal glucose tolerance, and absence of a T1D-protective HLA haplotype were enrolled in an oral insulin study very similar to DPT-1. Between 2007 and 2015, TrialNet enrolled 561 relatives of individuals with T1D who had ≥2 T1D autoantibodies, normal glucose tolerance, and absence of a T1D-protective HLA haplotype were enrolled in an oral insulin study very similar to DPT-1. This was a placebo-controlled trial comparing 7.5 mg/day of oral insulin to placebo in at-risk relatives. Primary outcome was time to T1D. Participants were divided into primary and secondary strata. The primary stratum (n=389) was intended for the primary outcome analysis. This group was confirmed to be IAA and ICA positive or positive for both GAD and IAA. This group had IAA ≥80 nU/mL, consistent with the post hoc analysis in DPT-1 suggesting that the subgroup of at-risk individuals in this category might have benefitted from oral insulin. Primary outcome showed that oral insulin at a dose of 7.5 mg/day for a mean of 2.7 years did not delay or prevent T1D development.[63]

Fr1da is a mechanistic study evaluating the immune efficacy of oral insulin in the secondary prevention of T1D. This study compares oral insulin to placebo in children ages 2 to 12 years with multiple T1D autoantibodies and normoglycemia. Those randomized to the active drug arm take 7.5 mg of oral insulin daily for 3 months followed by 67.5 mg daily for 9 months. Participants are evaluated every 6 months for at least 24 months. Primary outcomes include evidence of immune response to insulin (salivary IgA antibodies to insulin, blood CD4+ T cell responses to insulin, T1D autoantibodies), the development of dysglycemia, and/or clinical T1D. This study started in 2015 and was completed in late 2024. Results are pending.[64]

Intranasal Insulin

An intranasal route of insulin administration was chosen for two studies to induce tolerance because compared with the oral route of administration, nasal administration has the advantage that antigen is delivered in an undegraded form directly to the mucosa. This has been shown to be a more effective way to deliver the antigen.[65]

The Intranasal Insulin Trial-I (INIT-I), performed in Australia, randomized 38 individuals (mean age 10.8 years) with at least one T1D autoantibody to treatment with intranasal insulin, 1.6 mg, or placebo. The intervention was given daily for 10 days, then twice weekly for 6 months. After 6 months, participants crossed over to either active treatment or placebo (whichever they did not receive previously). Primary outcome was FPIR, a measure of β-cell function. This pilot study demonstrated that intranasal insulin induced immune changes suggestive of mucosal tolerance to insulin, slowing progression to clinical T1D. Further, intranasal insulin did not accelerate loss of β-cell function in at-risk individuals.[66]

In 2008, Näntö-Salonen et al published results from DIPP. The DIPP study evaluated the effect of nasal insulin on incidence of T1D in children from the general population who had genotypes and autoantibodies increasing their risk for T1D development. Participants were identified by analysis of cord blood samples for HLA-susceptible alleles for T1D. Those with genetic risk who consented to be screened for T1D autoantibodies were tested, and individuals with two or more autoantibodies were offered study participation. In addition, their siblings were offered screening, and if positive for at-risk HLA alleles and two or more T1D autoantibodies, they were also offered study inclusion. Enrolled individuals were treated with either 1 unit/kg of short-acting human insulin intranasally daily (n=137) or placebo (n=127). Primary endpoint was T1D diagnosis. Mean duration of treatment was 1.8 years. This study was terminated early for futility. There was no evidence for the delay or prevention of T1D due to the administration of intranasal insulin.[67]

The Intranasal Insulin Trial-II (INIT-II), a follow-up to INIT-I, enrolled 110 first- or second-degree relatives of people with T1D who were diagnosed prior to age 40. Participants had to be between 4- and 30-years-old if they had a first-degree relative with T1D and 4 to 20 years if they had a second-degree relative with T1D. They were required to have normal oral glucose tolerance, two or more T1D autoantibodies, and normal FPIR. Participants were randomized to receive either intranasal insulin (440 IU) or placebo daily for 7 days and then weekly for 12 months. Follow-up was performed for a total of 10 years. Primary outcome for this study was the diagnosis of clinical T1D. The INIT-II study was completed in late 2019, and while results have not yet been formally published, an abstract stated that there was no difference in the rate of progression to T1D between the intranasal insulin and placebo groups.[68,69]

Teplizumab

Immune interventions studied in individuals with recent-onset T1D have been shown to delay further loss of β-cell function.[70] This was true for the Fc receptor-nonbinding anti-CD3 monoclonal antibody teplizumab, which was

shown to reduce β-cell loss for as long as 7 years after diagnosis.[71-75]

TrialNet conducted a randomized, placebo-controlled, double-blind teplizumab trial. They enrolled 76 relatives of patients with T1D who were at high risk for development of clinical disease (≥2 T1D autoantibodies and dysglycemia). Participants were assigned to a 14-day course of teplizumab infusions or placebo, and were followed to primary outcome, T1D, with oral glucose tolerance testing every 6 months. Results from this study, reported in 2019, demonstrated delayed progression to clinical T1D in the active treatment group. Median time to T1D diagnosis was 48.4 months in the teplizumab treatment group and 24.4 months in the placebo group.[76] In 2021, Sims et al published extended follow-up data on the TrialNet teplizumab prevention study. Median times to T1D diagnosis were extended to 59.6 months in the teplizumab treatment group and 27.1 months for the placebo group, and 50% of the teplizumab-treated group remained clinical diabetes free, while only 22% of the placebo-treated group was still without clinical diabetes. On December 17, 2022, the U.S. Food and Drug Administration approved teplizumab (Tzield®) infusions to delay the onset of stage 3 T1D in adults and children ≥8 years with stage 2 T1D.[77]

Incretin

It has been proposed that β-cell stress contributes to the immune destruction of β-cells in the setting of progression to T1D.[78,79] Studies using the glucagon-like peptide-1 (GLP-1) analogue exendin-4 have demonstrated decreased β-cell stress and delayed T1D onset in the NOD mouse model.[80,81] In addition, a study in individuals with new-onset T1D utilizing anti-interleukin-21 antibody (anti-IL-21) and liraglutide, another GLP-1 analogue, showed that these two agents slowed β-cell loss when used together.[82]

In 2015, Kero et al launched the InnoVative Efficacy, Safety, and Tolerability (INVESTDIA) study, which hypothesized that liraglutide treatment would preserve β-cell function in individuals with multiple T1D autoantibodies with or without dysglycemia. They recruited T1D autoantibody positive participants from DIPP, TrialNet, and TEDDY as well as people with newly-diagnosed T1D from the Finnish Pediatric Diabetes Register for this study in stage 1, stage 2, and early stage 3 T1D. Participants (ages 10 to 30 years for stages 2 and 3 and ages 18 to 30 years for stage 1) were randomized to receive either liraglutide (0.6 mg subcutaneously daily with gradual increase to 1.8 mg daily) or placebo. Primary endpoint was β-cell function after 6 months of treatment as measured by FPIR during intravenous glucose tolerance test in stages 1 and 2 and C-peptide during a mixed meal tolerance test (MMTT) in stage 3. The stage 1 study started in 2015, and its outcome status is not reported. The stage 2 and 3 studies started in 2016 and were completed in 2021, but results have not been published to date.[83]

Hydroxychloroquine

Hydroxychloroquine, an antimalarial drug, is used to treat rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and other inflammatory rheumatic diseases in adults as well as young children. Studies have shown that hydroxychloroquine partially protected against streptozotocin-induced T1D in a rat model.[84] In addition, hydroxychloroquine reduced rates of diabetes in individuals with RA and SLE.[85-88] Hydroxychloroquine has also been associated with improved insulin sensitivity and β-cell function in a trial in overweight/obese adults without diabetes.[89] This data suggested that hydroxychloroquine could be beneficial for preventing T1D progression in its early stages.

In 2023, TrialNet published results from a double-blind, placebo-controlled trial of hydroxychloroquine in individuals with stage 1 T1D (≥2 T1D autoantibodies and normoglycemia). Participants, 273 relatives of individuals with stage 1 T1D, were treated with either hydroxychloroquine (n=183), 5 mg/kg daily to a maximum of 400 mg, or placebo (n=90). Enrollment was open to individuals ≥3 years of age. Primary outcome was rate of progression from stage 1 to stage 2 (≥2 T1D autoantibodies and dysglycemia) or 3 (clinical) T1D. After a median follow-up of 23.3 months, the trial was stopped early due to futility, and it was concluded that hydroxychloroquine did not delay progression to stage 2/3 T1D in individuals with stage 1 disease.[90]

Abatacept

Abatacept is a selective co-stimulation modulator that inhibits T cell activation by binding to CD80 and CD86 to block interaction with CD28. Abatacept's blockade of T cell activation was shown by TrialNet in a double-blind, placebo-controlled trial to slow β-cell loss in stage 3 (new-onset) T1D.[91,92] TrialNet subsequently conducted a phase 2 randomized, placebo-controlled, double-blind study of abatacept in stage 1 T1D. Participants were relatives of people with T1D between the ages of 6 and 45 years. They had ≥2 T1D autoantibodies and normoglycemia. The study randomized 212 individuals who met this criteria to receive infusions of either abatacept, 10 mg/kg (maximum 1,000 mg), or placebo at baseline, 2 weeks, 4 weeks, and monthly for a total of 1 year. Primary endpoint was incidence of progression to stage 2 or stage 3 T1D. Abatacept did not significantly delay progression, but did affect subsets of immune cells (as expected) and increased C-peptide response (preserved insulin secretion), implying that co-stimulation blockade might modify the progression of T1D.[93]

Glutamic Acid Decarboxylase

Glutamic Acid Decarboxylase (GAD) is an important autoantigen in individuals with T1D, and studies in animal models of autoimmunity have shown that treatment with a target antigen can modulate aggressive autoimmunity.[94] Diamyd®, a Swedish company focused on advancing precision medicine therapies for T1D, developed alum-formulated GAD65 (GAD-alum), which has been used in trials targeting the progression of T1D. Studies focusing on individuals with new-onset T1D have been done in addition to secondary prevention trials utilizing GAD-alum.

In 2008, Ludvigsson et al published results of a study that randomized 70 individuals, ages 10 to 18 years, diagnosed with T1D during the prior 18 months to receive

either GAD-alum, 20 µg by subcutaneous injection, or placebo on study days 1 and 30. Participants were required to have fasting C-peptide levels >0.1 nmol/L (0.3 ng/mL) and GAD autoantibodies at the time of randomization. Primary outcome, change in fasting C-peptide between baseline and month 15, demonstrated that GAD-alum as administered did not have a significant effect.[95]

TrialNet published results from a randomized, placebo-controlled study of the same GAD-alum preparation in individuals diagnosed with T1D during the prior 100 days, ages 3 to 45 years. They randomized 145 people who were positive for GAD autoantibodies and had stimulated C-peptide levels ≥0.2 nmol/L (0.6 ng/mL) to either 20 µg of GAD-alum or placebo (alum alone) subcutaneously at baseline and 4 weeks or at baseline, 4 weeks, and 12 weeks. Primary outcome was baseline-adjusted stimulated C-peptide area under the curve (AUC) over the first two hours of a MMTT at the 12 month visit. In 2011, Wherrett et al published the results of this trial, which demonstrated no difference between GAD-alum (both dosing regimens) and placebo treatment with respect to loss of insulin secretion.[96]

In 2017, Ludvigsson et al published results of a trial that administered GAD-alum autoantigen directly into an inguinal lymph node rather than injecting it subcutaneously, as this was thought to be a more efficient way to present antigen to the T cells. The study group also added oral vitamin D therapy as an immune modulator. This trial, GAD-Alum [Diamyd] Administered into Lymph Nodes in Combination with Vitamin D in Type 1 Diabetes (DIAGNODE-1), was an open-label pilot in 6 participants, ages 20 to 22 years, who had T1D for <6 months. All were GAD autoantibody positive and had fasting C-peptide levels >0.12 nmol/L (0.36 ng/mL). The GAD-alum, 4 µg, was injected into an inguinal lymph node using direct ultrasound guidance at baseline, 1 month, and 2 months. Participants also received an oral solution of Vitamin D (2,000 IU/day) for 4 months starting 1 month before the first GAD-alum injection. At 6 months, fasting and stimulated C-peptide levels did not decrease in any of the participants. At 15 months, C-peptide AUC was stable in 4 of the 6 participants with an increase of 34% in fasting C-peptide. HbA1c and insulin dose decreased in each participant. The investigators concluded that direct injection of GAD-alum into the lymph node with oral vitamin D administration was associated with preservation of residual β-cell function in the 6 participants studied.[97]

Ludvigsson et al subsequently performed a double-blind, placebo-controlled trial with a comparable regimen. The study randomized 109 individuals, ages 12 to 24 years, with T1D duration of 7 to 193 days, elevated serum GAD autoantibodies, and fasting serum C-peptide >0.12 nmol/L (0.36 ng/mL), to receive either 3 intralymphatic injections of GAD-alum (4 µg given 1 month apart) and oral vitamin D (2,000 IU daily for 120 days) or placebo. Primary outcome was change in stimulated serum C-peptide AUC between baseline and 15 months. The trial failed to demonstrate a significant difference between the treatment groups at 15 months. However, GAD-alum-treated individuals who had a high risk T1D genotype (HLA DR3-DQ2, n=29) showed greater stimulated C-peptide AUC preservation compared to those with the same genotype who were treated with placebo (n=17). In addition, continuous glucose monitor (CGM) recordings from most DR3-DQ2 participants (27 GAD-alum treated and 15 placebo treated) showed that time in range declined less over the course of the study in the GAD-alum treatment group and that those treated with GAD-alum had less glycemic variability.[98,99]

In 2018, Larsson et al published results from the first secondary prevention trial evaluating the efficacy of GAD-alum. The Diabetes Prevention-Immune Tolerance (DiAPREVIT) study enrolled 50 children, ages 4 to 17.9 years, with GAD autoantibodies, at least one other T1D autoantibody, and normoglycemia (stage 1 T1D) into a double-blind, placebo-controlled trial comparing 2 injections of GAD-alum (20 µg) or placebo given subcutaneously 30 days apart. Primary outcome, cumulative incidence of T1D over 5 years of follow-up, failed to show a significant improvement in time to clinical T1D diagnosis in the GAD-alum treatment group compared to placebo.[100]

In mid-2024, Diamyd® launched DiaPrecise, a GAD-alum secondary prevention study. DiaPrecise is an open-label, randomized clinical trial involving administration of either 2 or 3 doses of GAD-alum (4 µg) one month apart directly into an inguinal lymph node. Participants will be between 8 and 18 years of age and will have either stage 1 or stage 2 T1D. They will also be required to have the HLA DR3-DQ2 high-risk T1D haplotype that was associated with a positive response to GAD-alum in the Ludvigsson study. The primary outcomes for this safety and feasibility trial, which is currently underway, are all safety-related. It is estimated that this study will be completed at the end of 2026.[101]

Cord Blood

Investigators conducting the open-label CORD study, launched in Australia in 2013, hypothesize that infusion of autologous cord blood cells will restore immune tolerance and prevent or lessen T1D development when reinfused into children at high risk for T1D. The CORD study group is screening and monitoring children (ages 1 to 12 years) with a relative with T1D for the development of T1D autoantibodies. Twenty children with ≥2 T1D autoantibodies and stored (autologous) cord blood that is adequate in quality and quantity will be recruited to undergo reinfusion of their autologous cord blood. The primary outcome, which is still pending, will be feasibility of recruitment and safety.[102]

Discussion

To date, T1D screening and prevention studies have primarily focused on relatives of individuals with T1D because people with a T1D relative have a 15-fold increase in risk for development of clinical disease.[2] TrialNet demonstrated that the positivity rate among family members of people with T1D is 5.5%, meaning that for every 100 family members screened, only 5-6 will have T1D autoantibodies. Further, of these, several will have only a single T1D autoantibody and thus may not be at risk for clinical disease. Therefore, for every 100 family members screened, ~2-3 will have multiple

T1D autoantibodies and will eventually progress to clinical (stage 3) T1D.[11]

Screening studies in both T1D relatives and the general population have demonstrated feasibility and utility and have provided important information regarding screening benefits. They have transformed T1D from a disease typically diagnosed at the time of significant clinical illness to a predictable, evolving, staged autoimmune disease. It has been clearly shown that once a person has ≥2 T1D autoantibodies, their lifetime risk for progression to clinical (stage 3) T1D approaches 100% regardless of whether they have an affected relative.[4,5] In 2017, ISPAD recommended T1D autoantibody screening for first-degree relatives of individuals with T1D. In 2022, ISPAD acknowledged the importance of general population screening as well as education and monitoring for all those found to be at risk for progression to clinical T1D. Once teplizumab was approved for the treatment of individuals with stage 2 diabetes, the WHO indicated that criteria for general population screening for T1D had now been met.[7] Despite these recommendations and acknowledgements, general population screening is not currently the standard of care.

While it is easier to identify individuals with stages 1 and 2 T1D by screening people with affected relatives because they are at the highest risk for disease development, 85 to 95% of those who develop T1D do not have a positive family history.[3] By screening only T1D relatives, most at-risk individuals are not being identified prior to clinical diagnosis. This is a significant problem because the identification of preclinical (stages 1 and 2) T1D has been shown to decrease: (1) the rate and severity of DKA at the onset of clinical T1D, (2) neurocognitive damage associated with DKA, (3) successive episodes of DKA, and (4) rate of subsequent severe hypoglycemic episodes and worse glycemic control.[6,7] In addition, early identification of preclinical T1D provides the opportunity for patients and families to adjust to the impending diagnosis, become educated about T1D and its management, and consider participation in clinical research studies focused on delaying and/or preventing progression to clinical disease. Also, those in stage 2 may be eligible for treatment with teplizumab, which is approved by the FDA for the delay of progression to stage 3 T1D.[8]

Screening studies of T1D relatives, including the BOX Family Study, TrialNet, INNODIA, and Type1Screen, evaluated large numbers of individuals and demonstrated that early onset of T1D is a strong marker of increased familial risk, an autoantibody positivity rate of 5.5-6.0% among family members, the feasibility and utility of at home screening methods, and a marked decrease in DKA at disease presentation in those with early T1D detection. These screening efforts have also served as a source of participants for T1D prevention studies.[9,11,14] Several general population screening studies have also generated important information about risk and T1D pathogenesis. The GPPAD study identified infants at high genetic risk for T1D, and some were enrolled in the GPPAD-POInT primary prevention trial of oral insulin, which is currently underway.[15,16] The DIPP study demonstrated that while family history is a significant risk factor for the development of T1D, age at seroconversion is not affected by family history.[17] Fr1da identified a 0.31% prevalence of T1D autoantibodies in general population children aged 2 to 5 years and demonstrated that diagnosing presymptomatic T1D and educating/monitoring those affected resulted in improved clinical presentation at T1D clinical onset.[22,23] T1Detect showed that at-home screening kits for the detection of T1D autoantibodies in the general population is feasible and achieves autoantibody detection rates comparable to in-person clinical screening programs.[2,5] The PrIMeD study at the University of Virginia used salivary DNA to generate genetic risk scores for T1D risk. They found no relationship between genetic risk and age of T1D onset.[24] The Barbara Davis Center ASK study showed that general population screening is both feasible and cost-effective.[25] Some general population screening studies are still underway.

Both primary and secondary prevention studies have been performed in individuals at risk for the development of T1D. Some of these studies, particularly those in primary prevention, relied on general population screening to identify participants. A vitamin D study, conducted by Wicklow and Tabak, demonstrated the ability to recruit a sufficient number of genetically at-risk babies and that the dose of vitamin D used was safe.[31] Chase et al performed a study of DHA supplementation in babies with genetic risk of T1D. They found the supplements to be safe but failed to show reduction in inflammatory cytokine production.[32] The FINDIA study evaluated delayed exposure to bovine insulin in infants at genetic risk for T1D and found that those receiving insulin-free cow's milk had a reduced incidence of T1D autoantibodies.[39] The BABYDIET study, which assessed the effect of delayed gluten introduction in genetically at-risk infants on T1D autoimmunity, failed to demonstrate a reduction in T1D autoantibody development and T1D with delayed gluten exposure.[44] The DIPP study, which recruited individuals from the general population with genetic risk, evaluated the effect of treatment with intranasal insulin on T1D development, and found no evidence for delay or prevention of T1D.[67] Most studies of T1D secondary prevention enrolled relatives of individuals with T1D or a combination of relatives and people identified from the general population.

Screening and prevention studies in both T1D relatives and the general population demonstrate the importance of identifying individuals with stage 1 and stage 2 T1D to prevent serious illness at the time of diagnosis as well as subsequent T1D sequelae. In addition, there is now an approved treatment to delay progression to stage 3 T1D in those with stage 2 disease. Accomplishing early identification requires screening in both relatives and the general population. This approach has been shown to be both feasible and cost-effective. The TEDDY study demonstrated that T1D autoantibodies in genetically at-risk individuals often appear at a very early age, with the first T1D autoantibodies typically appearing between 1 and 3 years of age.[103,104] Therefore, it makes sense to take an approach such as that being used in the Israeli ADIR study, which tests children for T1D autoantibodies at the time of their scheduled primary care physician hemoglobin screenings at 9-18 months and

5 years.[5] This method avoids additional blood draws for patients and provides important information about T1D autoimmunity at appropriate ages. Children who test positive for ≥2 T1D autoantibodies should begin regular monitoring for staging and T1D progression, and families should be educated regarding the eventual diagnosis of clinical (stage 3) T1D. Because risk is higher in relatives of individuals with T1D, in addition to this general screening approach, relatives should be screened early and at regular intervals (every 1-2 years).

Conclusion

General population screening for pre-symptomatic (stages 1 and 2) T1D should be standard of care. Most new cases of clinical T1D arise in people without affected relatives, so screening only relatives of individuals with T1D is not sufficient. Identification of stage 1 and stage 2 T1D with subsequent monitoring significantly decreases DKA, a potentially life-threatening illness, at clinical diagnosis as well as additional disease sequelae. In addition, it provides those at risk with the opportunity to participate in clinical trials aimed at delaying and preventing progression to clinical T1D. Also, for those with stage 2 disease, there is an approved medication, teplizumab, that has been shown to delay progression to stage 3 (clinical) T1D. General population screening has been shown to be feasible and cost-effective and should be incorporated into the routine care provided by pediatric primary care practitioners.

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