Screening for Autoantibodies in Type 1 Diabetes: A Call to Action

Anne Peters, MD

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KEY TAKEAWAYS

- Type 1 diabetes (T1D) is an autoimmune disease that progresses through 3 distinct stages.
- T1D can be diagnosed at any age, with a peak incidence at 10-14 years of age.
- The incidence of T1D in the United States is rising.
- Screening for T1D autoantibodies has positive clinical consequences, including reduction of diabetic ketoacidosis events, improved glycemic control, and positive impact on short- and long-term complications.
- Primary care clinicians can play a critical role in promoting islet autoantibody screening.

FACULTY

Anne Peters, MD, Professor of Clinical Medicine, Keck School of Medicine of USC, Los Angeles, California.

DISCLOSURES

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The lack of therapeutic interventions to prevent progression of autoantibody-positive presymptomatic patients to clinical symptomatic type 1 diabetes (T1D) has meant that screening asymptomatic individuals for T1D is not commonly done. For instance, in 2015, the US Preventive Services Task Force recommended against performing routine serum islet autoantibody screening for T1D.[1] Nevertheless, results from the more recent Fr1da study[2,3] (see below) suggest that substantial health benefits may accrue from general population screening for islet autoantibodies. However, general population screening is costly, difficult to implement, and requires a significant commitment of time and resources. On the other hand, targeted screening of the at-risk population (ie, those with first- or second-degree relatives with T1D) zeroes in on a population more likely to have detectable islet autoantibodies. As such, the primary focus of this article is at-risk population screening. With the prospect of therapeutic agents that can potentially modify the autoimmune progression leading to clinical symptomatic T1D, the potential benefits of screening are mounting. Even though such therapeutic agents are not yet available, identifying the presence of islet autoantibodies has potential short- and long-term health benefits. This article will discuss the epidemiology, autoimmune basis, and natural history of T1D; the benefits of early detection; immunologic markers; and most importantly, the vital role that family and primary care clinicians can play in educating families about islet autoantibody screening.

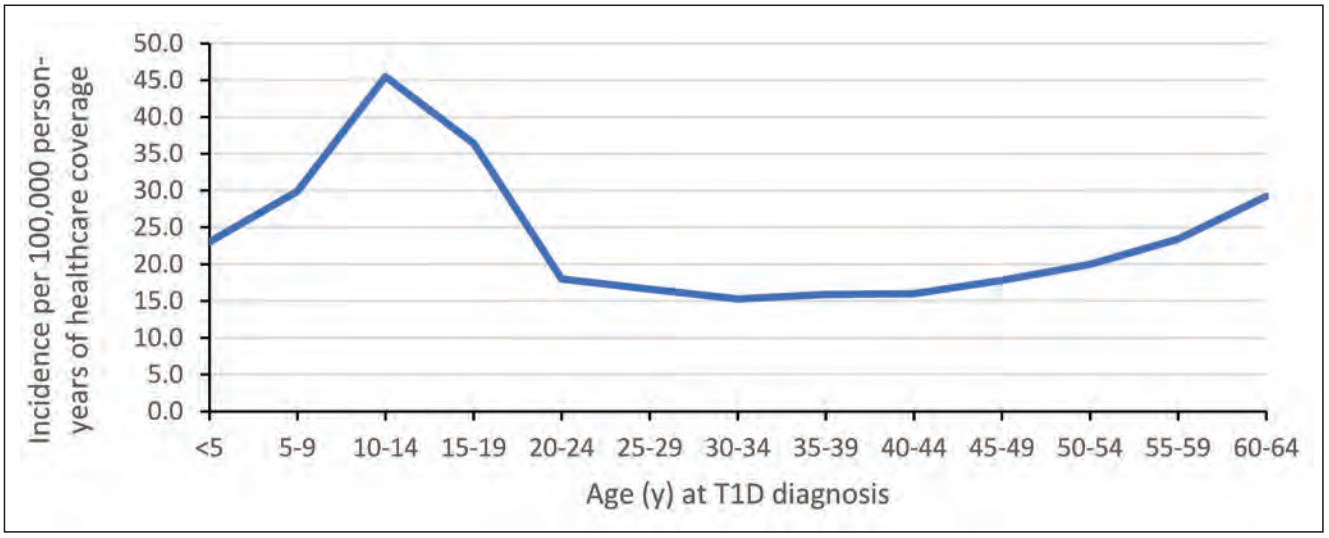
EPIDEMIOLOGY OF T1D

Nearly 190,000 children and adolescents have been diagnosed with T1D,[4] making it one of the most common chronic diseases in childhood.[5] Analyses of the SEARCH for Diabetes in Youth registry and Clinformatics Data Mart database showed that the incidence of T1D in youth (age 0 to 19 years) increased at an annual rate of 1.9% from 2001-2002 to 2015, with the incidence peaking in 10- to 14-year-olds **(FIGURE)**.[6,7] While T1D is generally thought of as a disease affecting only children, analysis of the Clinformatics Data Mart database showed that 59% of incident T1D cases were actually diagnosed in adults aged 20 to 64 years.[7]

AUTOIMMUNE BASIS OF T1D

More than 40 years ago, multiple lines of clinical evidence established an autoimmune pathogenesis for T1D leading to partial, or in many cases absolute, insulin deficiency.[8-11]

FIGURE. **Incidence of type 1 diabetes mellitus by age, 2001-2015**[7]



Although detection of serum islet autoantibodies against pancreatic B-cells is diagnostic for T1D, T1D is typically diagnosed based on clinical symptomatology associated with overt hyperglycemia, metabolic imbalance, and, in many cases, diabetic ketoacidosis (DKA).[12] Recent evidence from the SEARCH for Diabetes in Youth registry shows that the prevalence of DKA at or near T1D diagnosis increased from 35.3% in 2010 to 40.6% in 2016, representing a 2% relative annual increase.[69] In asymptomatic individuals, the development of islet autoantibodies against multiple β-cell antigens indicates a high probability of developing clinically symptomatic T1D (description of T1D disease stages to follow).

Genetics plays a key role in the pathogenesis of T1D, as demonstrated by the fact that the risk for autoimmunity and subsequent development of T1D is up to 10-fold higher in children with a first-degree relative with T1D as compared to children in the general population.[13] Some statistics worth noting are as follows. First, the prevalence of T1D at age 20 years in individuals of European descent is 2% for a child of a mother with T1D and 6% if the father has T1D.[14-16] The lifetime risk may be as high as 50% in individuals with multiple first-degree relatives with T1D.[16-18] The lifetime risk of T1D for a person with an identical twin with T1D may be as high as 60%.[19] For a non-twin sibling, the risk is 4% to 7% by age 20 years and 10% by age 60 years.[19]

Certain human leukocyte antigen (HLA) subtypes, particularly DR and DQ, can increase susceptibility or confer protection against development of T1D.[16,20] Smaller contributions are made by more than 50 non-HLA genes or loci.[12,21-28] The majority of individuals with T1D carry DR4, DQB*0302 and/or DR3, DQB*0201 and are considered genetically at risk for clinical T1D. Conversely, HLA alleles such as DQB1*0602 are associated with dominant protection from T1D.[29]

Nonetheless, only 10% to 20% of cases of T1D occur in individuals with a family history of T1D,[30,31] indicating that other factors play a key role in the pathogenesis of T1D. A wide variety of environmental factors have been proposed as being associated with the development of islet autoantibodies and subsequent T1D, but evidence is often conflicting.[32,33] Some data suggest that high birthweight for gestational age,[34] prematurity,[34] and higher rate of weight gain in early childhood may contribute.[35] Additional evidence suggests that the development of some autoantibodies may be preceded by changes in nutrition intake[36,37] or depend on the individual's metabolic profile.[38]

Notably, early childhood infections seem to play an important role in the development of islet autoimmunity.[39] These include recent respiratory infections such as common cold, influenza-like illness, sinusitis, and laryngitis/tracheitis,[40] as well as enteroviruses, particularly coxsackievirus types A and B.[41] Detection of enteroviruses in stools and circulating antivirus neutralizing antibodies precedes the appearance of islet autoantibodies by several months in children at increased genetic risk for T1D.[42-44] Furthermore, islet autoantibody-positive children with enterovirus RNA in their blood experience faster progression to T1D.[45]

NATURAL HISTORY OF T1D

Following the onset of islet autoimmunity, T1D progresses through 3 stages **(TABLE)**.[12,46] Stage 1 occurs in individuals who have developed ≥2 types of islet autoantibodies asso-

TABLE. **Metabolic stages of type 1 diabetes mellitus**[12,46]

	Stage 1	Stage 2	Stage 3
β-cell autoimmunity?	Yes	Yes	Yes
Symptoms?	No	No	Yes
Blood glucose	No IGT or IFG	• IGT and/or IFG • FPG 100-125 mg/dL • 2-h PPG 140-199 mg/dL • A1c 5.7%-6.4% or ≥10% increase in A1c	• Random glucose ≥200 mg/dL with symptoms • FPG ≥126 mg/dL • 2-h PPG ≥200 mg/dL • A1c ≥6.5%
5-y risk of symptomatic disease	44%	75%	–

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PPG, postprandial glucose.

ciated with T1D but remain normoglycemic. As functional pancreatic β-cell mass declines, progression to stage 2 occurs. Although individuals remain asymptomatic, evidence of dysglycemia emerges. Dysglycemia is defined as fasting plasma glucose (FPG) of 110 to <126 mg/dL, 2-hour oral glucose tolerance test (OGTT) of 140-199 mg/dL, and glycated hemoglobin (A1c) of 5.7%-6.4%. Further β-cell damage results in symptomatic stage 3 T1D, which is characterized by the typical symptoms and signs of diabetes, eg, polyuria, polydipsia, weight loss, and fatigue, corresponding to an FPG >126 mg/dL, 2-hour OGTT >200 mg/dL, and A1c >6.5%. If not treated with timely administration of exogenous insulin, it can quickly progress to DKA. DKA on presentation occurs in approximately one-third of individuals[6] and is often characterized by nausea, vomiting, abdominal pain, weakness, and confusion.

Approximately 70% of individuals with ≥2 islet autoantibodies progress from stage 1 to symptomatic stage 3 within 10 years[47] and 74% from stage 2 to symptomatic stage 3 within 4 to 5 years, although progression can be as short as weeks and as long as decades. It is important to note that individuals with 1 islet autoantibody may never progress to multiple autoantibodies (stage 1 or 2) and, ultimately, symptomatic stage 3 T1D. Although there are no guidelines for monitoring individuals with only 1 islet autoantibody, annual evaluation for dysglycemia or additional islet autoantibody testing every 1 to 2 years should be considered given their increased risk. In rare cases, loss of islet autoantibody positivity is observed, also referred to as inverse seroconversion.[3]

BENEFITS OF EARLY DETECTION OF AT-RISK INDIVIDUALS

Several clinical trials have investigated the impact of early detection of T1D in at-risk individuals, as well as the general population. One of the first was the Diabetes Autoimmunity Study in the Young (DAISY), a longitudinal study that followed children with either a family history of T1D (at-risk) or who expressed high-risk HLA genotypes.[48] Children identified as multiple islet autoantibody–positive and followed to symptomatic stage 3 T1D were hospitalized significantly less often than the T1D cases from the general population (3.3% vs 44%). Additionally, they had a lower mean A1c at T1D diagnosis (7.2% vs 10.9%; $P<0.0001$) and 1 month after diagnosis (6.9% vs 8.6%; $P<0.0001$), but not 6 months or 12 months after diagnosis due to the initiation of insulin therapy in the general population cohort. A major finding of the DAISY study was a decrease in hospitalizations due to DKA, which has significant long-term sequelae.

The BABYDIAB and the Munich Family Study followed children with a first-degree family member (at-risk) with a history of T1D. Data from these German databases were analyzed by the Diabetes Prospective Documentation Initiative.[49] Among the 101 children screened and found to be positive for islet autoantibodies, the A1c at symptomatic stage 3 T1D onset was significantly lower than in non-screened children presenting with symptomatic stage 3 T1D (8.6% vs 11%). In addition, the prevalence of DKA was significantly lower in screened children (3.3% vs 29.1%) and was associated with a significantly shorter hospitalization period at onset (11.4 vs 14.9 days).

Recently, the results of the German Fr1da study demonstrated important benefits with population-based screening for islet autoantibodies.[3] Screening was offered to children ages 1.75 to 5.99 years by pediatricians during well-baby visits. Of 90,632 children screened (median age 3.1 years), 196 (0.22%) were found to be in stage 1, 17 (0.02%) in stage 2, and 26 (0.03%) in symptomatic stage 3, for an overall prevalence of 0.31%; 41 children with a family history of multiple islet autoantibodies declined metabolic staging. Over 3 years of follow-up, the risk of progressing from stage 1 to stage 2 or 3 was 28.7%. Key factors significantly associated with disease progression were obesity, presence of 4 islet autoantibodies,

and A1c ≥5.7%. The study showed that preschool screening for islet autoantibodies in the general population effectively identified young children with previously undiagnosed, symptomatic stage 3 T1D.

The Fr1da study also showed that psychological stress was significantly higher in mothers of children identified as having stage 1 or 2 T1D compared with mothers of children without islet autoantibodies. The stress level decreased to baseline within 12 months of identification. Of the 62 children with stage 1 or 2 T1D who progressed to symptomatic stage 3, only 2 presented with mild or moderate DKA, both without clinical symptoms. The decline in psychological stress and the low incidence of DKA were predicted, since >80% of children with stage 1 or 2 T1D and their families participated in the diabetes education program.

These investigations demonstrate that early identification of individuals with stage 1 and 2 T1D allows for early intervention that results in reduced morbidity and improved glycemic control. An additional possible benefit of early detection of stage 1 or 2 T1D is that it might enable earlier intervention to mitigate common chronic complications of T1D that begin to emerge within months or years of diagnosis. For example, the SEARCH for Diabetes in Youth Study showed that several complications were common in youth and young adults with T1D at a mean disease duration of 8 years. These were cardiovascular autonomic neuropathy (14.4%), arterial stiffness (11.6%), hypertension (10.1%), peripheral neuropathy (8.5%), diabetic kidney disease (5.8%), and retinopathy (5.6%).[6]

The occurrence of DKA at symptomatic stage 3 T1D diagnosis results in additional complications. One investigation showed that children ages 6 to 18 years with DKA at symptomatic stage 3 T1D diagnosis experienced a decrease in total white matter volume and an increase in gray matter over 6 months, changes that were associated with adverse neurocognitive outcomes.[50] DKA at diagnosis of symptomatic stage 3 T1D also adversely affects long-term glycemic control.[51] A prospective study of 3364 children diagnosed with symptomatic stage 3 T1D before 18 years of age and followed for 15 years found that the A1c was 1.4% higher in those with severe DKA at diagnosis compared with children without DKA at diagnosis.[51]

Finally, the cost-effectiveness of islet autoantibody screening of the general population for T1D risk has been investigated in 2 studies.[52,53] One study based cost-effectiveness on reducing the incidence of DKA at symptomatic stage 3 diagnosis in children age <5 years,[52] while the other based cost-effectiveness on reduction in DKA events and long-term glycemic control.[53] Although neither study found screening the general population for islet autoantibodies to be cost-effective, no consideration was given to other possible benefits of early detection such as reducing long-term sequalae of having DKA at time of symptomatic stage 3 T1D diagnosis (as highlighted earlier). In contrast, data from the Autoimmunity Screening for Kids (ASK) study in Colorado determined that general population screening for islet autoantibodies is feasible and well accepted by parents and providers.

METABOLIC MARKERS

A variety of genetic, immunologic, and metabolic markers may be used to predict T1D. Among metabolic markers, the first-phase insulin response to glucose during an intravenous glucose tolerance test[54] and 2-hour OGTT[55] are useful to identify autoantibody-positive individuals who are at highest risk for progressing to T1D. Recent investigation confirmed that worsening longitudinal changes in the glucose response curve during OGTT occur in individuals who progress to T1D.[56] Individuals with undiagnosed clinical T1D (stage 3) may be identified using common metabolic tests, eg, random plasma glucose >200 mg/dL and A1c ≥6.5%.

PRACTICAL CONSIDERATIONS FOR ISLET AUTOANTIBODY TESTING

Symptomatic stage 3 T1D is preceded by the development of autoantibodies against pancreatic β-cell antigens. The most commonly studied and measured islet autoantibodies are islet cell antibodies (ICAs), insulin autoantibodies (IAAs), glutamic acid decarboxylase autoantibodies (GADAs), insulinoma-associated antigen-2 autoantibodies (IA-2As), and zinc transporter 8 autoantibodies (ZnT8As).[57-59] It should be noted that ICAs are not specific for T1D and not generally used for T1D screening.[60] Children who develop islet autoantibodies before age 2 years usually exhibit ZnT8As and IAAs first, while individuals who develop autoantibodies during preschool are more likely to exhibit IA-2As and GADAs first.[61,62] At the time of T1D diagnosis, 50% to 90% of individuals are IAA-positive, 50% to 80% GAAD-positive, 50% to 70% ZnT8A-positive, and 30% to 70% IA-2A-positive.[63]

A panel of several of the most common autoantibodies, ie, IAA, GAAD, IA-2A, and ZnT8A, should be used rather than individual antibody tests.[46,64,65] This strategy is beneficial for several reasons. First, an individual may be positive for only 1 autoantibody early in the disease course and would be missed without performing the complete panel. Second, the islet autoantibody profiles of individuals who progress to symptomatic stage 3 T1D vary. A diagnosis of T1D can be made only when 2 or more autoantibodies persist.

OPTIONS FOR AUTOANTIBODY SCREENING

Panels for screening are accessible to clinicians through

commercial labs, as well as programs such as those being offered through the JDRF T1Detect program (https://www.jdrf.org/t1d-resources/t1detect/), or for research purposes through TrialNet (https://www.trialnet.org/participate). The T1Detect program is a population screening education and awareness program for early detection of people with stage 1 or stage 2 T1D launched in December 2020.[66] The intent is to decrease the incidence of DKA and help those at risk of progressing to symptomatic stage 3 and their families develop a plan for further monitoring. Reducing the risk of DKA was recently found to be of paramount importance to parents with and without children with T1D in the United States.[67]

RECOMMENDATIONS FOR SCREENING

Currently, there are no universally agreed-upon recommendations for islet autoantibody screening for T1D outside of the research setting. The guidelines of multiple professional organizations including the American Diabetes Association, International Society for Pediatric and Adolescent Diabetes, and European Society for Paediatric Endocrinology do not recommend screening for autoantibodies as standard of care, but rather call for them to be performed only within the context of a clinical trial. Although the stated rationale for this approach is the lack of approved therapeutic options to prevent progression to symptomatic stage 3, the landscape is rapidly changing, with several investigational agents currently in late-stage development or under review by the US Food and Drug Administration and other regulatory bodies. Perhaps more importantly, there are data demonstrating reduction of DKA in both population and high-risk individual screening programs. In addition to the immediate life-threatening complications of DKA, correlations exist with poorer long-term glycemic outcomes, making the argument to screen compelling. The aspirational goal of population screening is important; however, implementation provides formidable challenges. In contrast, islet autoantibody screening of those at risk, who have a 10-fold-greater risk of developing symptomatic stage 3 T1D in their lifetime, is achievable today.

ROLE OF PRIMARY CARE CLINICIANS IN SCREENING AT-RISK INDIVIDUALS

As the primary healthcare clinicians for children and adolescents, family physicians and pediatricians are the anchor of their overall healthcare. Consequently, family physicians and pediatricians are likely to be the first point of contact when a child with T1D becomes clinically symptomatic (stage 3 T1D). Given the intimacy and familiarity with the family and caregivers, the impact that these clinicians can have on promoting awareness of the option and rationale to screen is unique. Screening can be performed in a variety of different settings, including the office, commercial labs, and at home. Moreover, because family physicians provide general care to adults with T1D,[68] they are in a key position to recommend screening of children, siblings, parents, and other relatives of their adult patients with T1D. Finally, more than half of incident cases of T1D are identified as adults; thus, family physicians should consider T1D in lean adults with evidence of hyperglycemia or those diagnosed with type 2 diabetes who progress rapidly to require insulin.

CONCLUSION

T1D is an autoimmune disease with 3 stages that can be identified through islet autoantibody screening. The likelihood of developing symptomatic stage 3 T1D approaches 100% in the presence of 2 or more antibodies. Detecting the antibodies in asymptomatic, high-risk patients has potential benefits including reductions in DKA events as well as short- and long-term complications. Family physicians and other primary care clinicians can play a unique role in their ability to promote and recommend the option of screening for families who are at risk for developing symptomatic stage 3 T1D. ●

REFERENCES

1. Siu AL. Screening for abnormal blood glucose and type 2 diabetes mellitus: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2015;163(11):861-868.
2. Raab J, Haupt F, Scholz M, et al. Capillary blood islet autoantibody screening for identifying pre-type 1 diabetes in the general population: design and initial results of the Fr1da study. *BMJ Open*. 2016;6(5):e011144.
3. Ziegler AG, Kick K, Bonifacio E, et al. Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. *JAMA*. 2020;323(4):339-351.
4. Centers for Disease Control and Prevention. National Diabetes Statistics Report 2020. Published 2020. Accessed February 26, 2020. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
5. Zylke JW, DeAngelis CD. Pediatric chronic diseases—stealing childhood. *JAMA*. 2007;297(24):2765-2766.
6. Dabelea D, Sauder KA, Jensen ET, et al. Twenty years of pediatric diabetes surveillance: what do we know and why it matters. *Ann N Y Acad Sci*. 2021. doi:10.1111/nyas.14573
7. Rogers MAM, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. *BMC Med*. 2017;15(1):199.
8. Gepts W. Pathologic anatomy of the pancreas in juvenile diabetes mellitus. *Diabetes*. 1965;14(10):619-633.
9. Nerup J, Platz P, Andersen OO, et al. HL-A antigens and diabetes mellitus. *Lancet*. 1974;2(7885):864-866.
10. MacCuish AC, Irvine WJ, Barnes EW, Duncan LJ. Antibodies to pancreatic islet cells in insulin-dependent diabetics with coexistent autoimmune disease. *Lancet*. 1974;2(7896):1529-1531.
11. Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet*. 1974;2(7892):1279-1283.
12. Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care*. 2015;38(10):1964-1974.
13. Hippich M, Beyerlein A, Hagopian WA, et al. Genetic contribution to the divergence in type 1 diabetes risk between children from the general population and children from affected families. *Diabetes*. 2019;68(4):847-857.
14. Warram JH, Krolewski AS, Gottlieb MS, Kahn CR. Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers. *N Engl J Med*. 1984;311(3):149-152.
15. Pociot F, Nørgaard K, Hobolth N, Andersen O, Nerup J. A nationwide population-based study of the familial aggregation of type 1 (insulin-dependent) diabetes mellitus in Denmark. Danish Study Group of Diabetes in Childhood. *Diabetologia*. 1993;36(9):870-875.
16. Bonifacio E. Predicting type 1 diabetes using biomarkers. *Diabetes Care*. 2015;38(6):989-996.
17. Tuomilehto J, Podar T, Tuomilehto-Wolf E, Virtala E. Evidence for importance of gender and birth cohort for risk of IDDM in offspring of IDDM parents. *Diabetologia*. 1995;38(8):975-982.

18. Guo SW, Tuomilehto J. Preferential transmission of type 1 diabetes from parents to offspring: fact or artifact? *Genet Epidemiol*. 2002;23(4):323-334.
19. Mayer-Davis EJ, Kahkoska AR, Jefferies C, et al. ISPAD Clinical Practice Consensus Guidelines 2018: definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. 2018;19(Suppl 27):7-19.
20. Noble JA, Valdes AM. Genetics of the HLA region in the prediction of type 1 diabetes. *Curr Diab Rep*. 2011;11(6):533-542.
21. Schenker M, Hummel M, Ferber K, et al. Early expression and high prevalence of islet autoantibodies for DR3/4 heterozygous and DR4/4 homozygous offspring of parents with Type I diabetes: the German BABYDIAB study. *Diabetologia*. 1999;42(6):671-677.
22. Hagopian WA, Erlich H, Lernmark A, et al. The Environmental Determinants of Diabetes in the Young (TEDDY): genetic criteria and international diabetes risk screening of 421 000 infants. *Pediatr Diabetes*. 2011;12(8):733-743.
23. Törn C, Hadley D, Lee HS, et al. Role of type 1 diabetes-associated SNPs on risk of autoantibody positivity in the TEDDY study. *Diabetes*. 2015;64(5):1818-1829.
24. Ziegler AG, Nepom GT. Prediction and pathogenesis in type 1 diabetes. *Immunity*. 2010;32(4):468-478.
25. Bonifacio E, Warncke K, Winkler C, Wallner M, Ziegler AG. Cesarean section and interferon-induced helicase gene polymorphisms combine to increase childhood type 1 diabetes risk. *Diabetes*. 2011;60(12):3300-3306.
26. Krischer JP, Liu X, Lernmark Å, et al. The influence of type 1 diabetes genetic susceptibility regions, age, sex, and family history on the progression from multiple autoantibodies to type 1 diabetes: a TEDDY study report. *Diabetes*. 2017;66(12):3122-3129.
27. Pöllänen PM, Lempainen J, Laine AP, et al. Characterisation of rapid progressors to type 1 diabetes among children with HLA-conferred disease susceptibility. *Diabetologia*. 2017;60(7):1284-1293.
28. Thomson G, Robinson WP, Kuhner MK, et al. Genetic heterogeneity, modes of inheritance, and risk estimates for a joint study of Caucasians with insulin-dependent diabetes mellitus. *Am J Hum Genet*. 1988;43(6):799-816.
29. Morran MP, Vonberg A, Khadra A, Pietropaolo M. Immunogenetics of type 1 diabetes mellitus. *Mol Aspects Med*. 2015;42:42-60.
30. Hemminki K, Li X, Sundquist J, Sundquist K. Familial association between type 1 diabetes and other autoimmune and related diseases. *Diabetologia*. 2009;52(9):1820-1828.
31. Parkkola A, Härkönen T, Ryhänen SJ, Ilonen J, Knip M. Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. *Diabetes Care*. 2013;36(2):348-354.
32. Hyöty H, Taylor KW. The role of viruses in human diabetes. *Diabetologia*. 2002;45(10):1353-1361.
33. Rewers M, Hyöty H, Lernmark Å, et al. The Environmental Determinants of Diabetes in the Young (TEDDY) Study: 2018 update. *Curr Diab Rep*. 2018;18(12):136.
34. Goldacre RR. Associations between birthweight, gestational age at birth and subsequent type 1 diabetes in children under 12: a retrospective cohort study in England, 1998-2012. *Diabetologia*. 2018;61(3):616-625.
35. Liu X, Vehik K, Huang Y, et al. Distinct growth phases in early life associated with the risk of type 1 diabetes: the TEDDY study. *Diabetes Care*. 2020;43(3):556-562.
36. Johnson RK, Vanderlinden LA, DeFelice BC, et al. Metabolomics-related nutrient patterns at seroconversion and risk of progression to type 1 diabetes. *Pediatr Diabetes*. 2020;21(7):1202-1209.
37. Li Q, Liu X, Yang J, et al. Plasma metabolome and circulating vitamins stratified onset age of an initial islet autoantibody and progression to type 1 diabetes: the TEDDY study. *Diabetes*. 2021;70(1):282-292.
38. Li Q, Parikh H, Butterworth MD, et al. Longitudinal metabolome-wide signals prior to the appearance of a first islet autoantibody in children participating in the TEDDY study. *Diabetes*. 2020;69(3):465-476.
39. Mustonen N, Siljander H, Peet A, et al. Early childhood infections precede development of beta-cell autoimmunity and type 1 diabetes in children with HLA-conferred disease risk. *Pediatr Diabetes*. 2018;19(2):293-299.
40. Lönnrot M, Lynch KF, Elding Larsson H, et al. Respiratory infections are temporally associated with initiation of type 1 diabetes autoimmunity: the TEDDY study. *Diabetologia*. 2017;60(10):1931-1940.
41. Sioofy-Khojine AB, Oikarinen S, Honkanen H, et al. Molecular epidemiology of enteroviruses in young children at increased risk of type 1 diabetes. *PLoS One*. 2018;13(9):e0201959.
42. Gamble DR, Taylor KW. Seasonal incidence of diabetes mellitus. *Br Med J*. 1969;3(5671):631-633.
43. Honkanen H, Oikarinen S, Nurminen N, et al. Detection of enteroviruses in stools precedes islet autoimmunity by several months: possible evidence for slowly operating mechanisms in virus-induced autoimmunity. *Diabetologia*. 2017;60(3):424-431.
44. Laitinen OH, Honkanen H, Pakkanen O, et al. Coxsackievirus B1 is associated with induction of β-cell autoimmunity that portends type 1 diabetes. *Diabetes*. 2014;63(2):446-455.
45. Stene LC, Oikarinen S, Hyöty H, et al. Enterovirus infection and progression from islet autoimmunity to type 1 diabetes: the Diabetes and Autoimmunity Study in the Young (DAISY). *Diabetes*. 2010;59(12):3174-3180.
46. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes–2021*. *Diabetes Care*. 2021;44(Suppl 1):S15-S33.
47. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA*. 2013;309(23):2473-2479.
48. Barker JM, Goehrig SH, Barriga K, et al. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care*. 2004;27(6):1399-1404.
49. Winkler C, Schober E, Ziegler AG, Holl RW. Markedly reduced rate of diabetic ketoacidosis at onset of type 1 diabetes in relatives screened for islet autoantibodies. *Pediatr Diabetes*. 2012;13(4):308-313.
50. Cameron FJ, Scratch SE, Nadebaum C, et al. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. *Diabetes Care*. 2014;37(6):1554-1562.
51. Duca LM, Wang B, Rewers M, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control. *Diabetes Care*. 2017;40(9):1249-1255.
52. Meehan C, Fout B, Ashcraft J, Schatz DA, Haller MJ. Screening for T1D risk to reduce DKA is not economically viable. *Pediatr Diabetes*. 2015;16(8):565-572.
53. McQueen RB, Geno Rasmussen C, Waugh K, et al. Cost and cost-effectiveness of large-scale screening for type 1 diabetes in Colorado. *Diabetes Care*. 2020;43(7):1496-1503.
54. Bingley PJ. Interactions of age, islet cell antibodies, insulin autoantibodies, and first-phase insulin response in predicting risk of progression to IDDM in ICA+ relatives: the ICARUS data set. Islet Cell Antibody Register Users Study. *Diabetes*. 1996;45(12):1720-1728.
55. Kanauchi M, Kimura K, Kanauchi K, Saito Y. Beta-cell function and insulin sensitivity contribute to the shape of plasma glucose curve during an oral glucose tolerance test in non-diabetic individuals. *Int J Clin Pract*. 2005;59(4):427-432.
56. Ismail HM, Cleves MA, Xu P, et al. The pathological evolution of glucose response curves during the progression to type 1 diabetes in the TrialNet Pathway to Prevention study. *Diabetes Care*. 2020;43(11):2668-2674.
57. Lawrence JM, Slezak JM, Quesenberry C, et al. Incidence and predictors of type 1 diabetes among younger adults aged 20-45 years: the diabetes in young adults (DiYA) study. *Diabetes Res Clin Pract*. 2021;171:108624.
58. Krischer JP, Liu X, Vehik K, et al. Predicting islet cell autoimmunity and type 1 diabetes: an 8-year TEDDY study progress report. *Diabetes Care*. 2019;42(6):1051-1060.
59. Regnell SE, Lernmark Å. Early prediction of autoimmune (type 1) diabetes. *Diabetologia*. 2017;60(8):1370-1381.
60. Simmons KM, Steck AK. Islet autoantibody testing. Current utility, future prospects in predicting and diagnosing type 1 diabetes. Published 2017. Accessed March 3, 2021. https://www.aacc.org/cln/articles/2017/july/islet-autoantibody-testing-predicting-and-diagnosing-type-1-diabetes
61. Ilonen J, Lempainen J, Hammais A, et al. Primary islet autoantibody at initial seroconversion and autoantibodies at diagnosis of type 1 diabetes as markers of disease heterogeneity. *Pediatr Diabetes*. 2018;19(2):284-292.
62. Pöllänen PM, Ryhänen SJ, Toppari J, et al. Dynamics of islet autoantibodies during prospective follow-up from birth to age 15 years. *J Clin Endocrinol Metab*. 2020;105(12):e4638-e4651.
63. Schlosser M, Mueller PW, Törn C, Bonifacio E, Bingley PJ. Diabetes Antibody Standardization Program: evaluation of assays for insulin autoantibodies. *Diabetologia*. 2010;53(12):2611-2620.
64. Tsai AC. 6 tests to determine diabetes type. *Diabetes Forecast*. 2015;68(5).
65. Simmons KM, Youngkin E, Alkanani A, et al. Screening children for type 1 diabetes-associated antibodies at community health fairs. *Pediatr Diabetes*. 2019;20(7):909-914.
66. JDRF. JDRF launches first mass screening program for early-stage type 1 diabetes (T1D) detection. Published 2020. Accessed March 1, 2021. https://www.jdrf.org/press-releases/jdrf-launches-first-mass-screening-program-for-early-stage-type-1-diabetes-t1d-detection/
67. Dunne JL, Koralova A, Sutphin J, et al. Parent and pediatrician preferences for type 1 diabetes screening in the U.S. *Diabetes Care*. 2021;44(2):332-339.
68. Romeo GR, Hirsch IB, Lash RW, Gabbay RA. Trends in the endocrinology fellowship recruitment: reasons for concern and possible interventions. *J Clin Endocrinol Metab*. 2020;105(6):1701-1706.
69. Jensen ET, Stafford JM, Saydah S, et al. Increase in prevalence of diabetic ketoacidosis at diagnosis among youth with type 1 diabetes: the SEARCH for Diabetes in Youth Study. *Diabetes Care*. 2021. doi:10.2337/dc20-0389