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THE RECENT RISE IN THE FREQUENCY OF TYPE 1 DIABETES: WHO PULLED THE TRIGGER?

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Keywords

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Type 1 Diabetes (T1D) is a chronic, autoimmune disorder characterized by T-cell infiltration and production of autoantibodies, targeted at pancreatic β-cells. The disease is thought to result from a complex interplay between genetic and environmental factors, leading to breakdown of tolerance [1,3]. T1D is one of the most common diseases among the pediatric population and its incidence is rapidly increasing [1,2]. The duration of the sudden rise in incidence in T1D is too short to be attributed to genetic effects, and it is likely caused by environmental factors; but which ones and by what mechanisms is still not known [4,5].

Many studies have provided evidence that ethnic background is an important risk factor for developing T1D, with Caucasians tending to be at higher overall risk than other racial groups [1–4]. In the USA, non-hispanic whites have an approximately 50% higher risk of developing T1D than African Americans or Hispanics (reviewed in [1]), [6]. The SEARCH study, performed on diabetic youths less than 20 years of age, aimed to identify the incidence and prevalence of T1D in the USA by age, sex, and race/ethnicity [6]. The prevalence of T1D among non-hispanic white youths was found to be 2.0/1000 and the incidence was 23.6/100,000 per year, with slightly higher rates for males compared to females [4,6]. These were concluded to be among the highest rates in the world for this population. The geographic areas with the highest incidence rates include Finland and Sardinia with >20/100,000 per year (reviewed in [4]). However, neighbouring areas of Finland, for example Estonia has a much lower incidence suggesting a role for genes and environment, or both (reviewed in [3]),[2]. The lowest overall incidence (<1/100,000 per year) has been reported in Chinese and South American populations [4,7]. Recently, studies have shown that the incidence appears to be increasing in almost all populations [8]. Results from the DIAMOND project, which examined trends in incidence from 1990 to 1999, revealed a worldwide increase in incidence in T1D (5.3% in North America, 4.0% in Asia, and 3.2% in Europe), except for Central America and the West Indies, where a decrease in incidence of 3.6% was noted (reviewed in [4]),[7]. In addition, the incidence rates of T1D increase with age with peak expression observed in those aged 10–14 years. However, there is now a shift to an earlier age of onset, with a more rapid increase in incidence being observed in younger children (ages < 5 years) [1]. The period of time over which T1D incidence increases is too short to attribute to genetic shifts, and a corresponding increase in the frequency of T1D risk genes (eg. MHC class II, insulin) has not been observed [9,10]. Therefore, it is likely that permissive environmental factors exert a stronger influence on this

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trend, resulting in increased disease penetrance in those with low-moderate risk HLA genotypes, when compared to individuals at higher genetic risk [1,2,4,11].

The environmental factors which are responsible for triggering autoimmunity to the β-cells and the mechanisms by which they cause disease remain unclear. Considering the higher prevalence of T1D in younger age groups, there is interest in environmental exposures that occur during the fetal, neonatal, and childhood periods. These factors include high birthweight, accelerated early growth, and early life feeding patterns, such as exposure to cow's milk [1,4,12]. Viruses (eg. Coxsackie virus and other enteroviruses) may also trigger autoimmunity or accelerate β–cell destruction and there is some evidence that seasonal variation coincides with the time of enterovirus infection [2,12]. Moreover, human enteroviruses have been identified in the pancreatic islets of T1D patients, suggesting direct interaction of the virus with islets and insulin producing β–cells [13]. Conversely, according to the hygiene hypothesis, lack of exposure to viruses or other pathogens can also increase T1D risk, by hindering maturation of the immune system [1,12]. Other non-genetic triggers include psychological stress, climatic influences, and environmental toxins (eg. N-nitroso derivatives), which may further modify the disease process [2]. More recently, the gut has been implicated as an initiator of autoimmunity leading to the development of T1D [14]. With three proposed facets (intestinal microbiota, altered gut permeability, and mucosal immunity), the data suggest that collection of unhealthy microbial flora can cause disruptions to the intestinal barrier, or a 'leaky gut', which produces specific immune responses ultimately resulting in pancreatic β-cell destruction [15]. If this hypothesis is confirmed, antibiotic treatment, and the administration of probiotics, could potentially be used therapeutically [1,15]. Vitamin D has also been associated with the pathogenesis of T1D since it may contribute to the maintenance of mucosal integrity and is beneficial in controlling gut permeability [1,15]. However, more extensive studies are awaited to further investigate these immunomodulators and the mechanisms by which they cause disease.

In the current issue of Journal of Autoimmunity, Ziegler and colleagues further investigate the escalating incidence of type 1 diabetes in young children [16]. In one of the most comprehensive studies to date focusing on the recent rise in incidence of T1D, the authors attribute the early onset in T1D to a faster progression from autoimmunity to disease, rather than an increase in the incidence of islet cell autoimmunity itself. Ziegler et al. studied two groups of children born in Germany, who were genetically predisposed to T1D, over a 20-year period. A total of 324 children (BABYDIAB study) born between 1989 and 2000, and 216 children (TEDDY study) born between 2004 and 2010, who were first degree relatives of patients with T1D, were recruited before the age of 3 months and prospectively followed from birth without intervention. Children with matched HLA genotypes were monitored for the development of antibodies to insulin, glutamic acid decarboxylase (GAD), and insulinoma-associated protein 2 (IA-2), as well as for progression to diabetes. Although the cumulative prevalence of islet autoantibodies by age 4 was similar in both groups of children, a higher cumulative frequency of diabetes was seen in the TEDDY study (6.2%) vs. the BABYDIAB study (2.5%). Additionally, a markedly increased progression to diabetes from the development of islet autoantibodies was observed in the TEDDY group, with 50% progression within 9.6 months vs. 85.2 months for the BABYDIAB cohort. The fact that the prevalence of autoantibodies, reflecting genetic susceptibility, did not differ between the two cohorts, but disease progression, reflecting environmental triggers, was significantly accelerated, underscores the importance of gene-environment interaction in the etiology of T1D. The question then arises as to how do genes and environment interact to trigger disease? Recently, it has been suggested that epigenetic effects underlie gene-environment interactions in triggering complex diseases [9,17]. Epigenetic effects are any non-DNA sequence encoded effects on gene expression and regulation. These include post-translational modifications of histones, DNA methylation, and microRNA expression, all of

which could be influenced by environmental factors, such as dietary antigens or viruses [9,18,19]. Epigenetic effects are usually long lasting after the original insult and could explain the accelerated progression of T1D reported by Ziegler et al. Whether the accelerated progression is due to an epigenetically driven heightened immune response, or increased β-cell dysfunction, or both is not known, and, hopefully, future research will address this important question.

References

1. Vehik K, Dabelea D. The changing epidemiology of type 1 diabetes: why is it going through the roof? Diabetes Metab Res Rev. 2011; 27:3–13. [PubMed: 21218503]
2. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet. 2001; 358:221–29. [PubMed: 11476858]
3. Huber A, Menconi F, Corathers S, Jacobson EM, Tomer Y. Joint Genetic Susceptibility to Type 1 Diabetes and Autoimmune Thyroiditis: from Epidemiology to Mechanisms. Endocr Rev. 2008; 29(6):697–725. [PubMed: 18776148]
4. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of Type 1 Diabetes. Endocrinol Metab Clin North Am. 2010; 39(3):481–497. [PubMed: 20723815]
5. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G. the EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. Lancet. 2009; 373(9680):2027–33. [PubMed: 19481249]
6. Mayer-Davis EJ, Bell RA, Dabelea D, D'Agostino R, Imperatore G, Lawrence JM, et al. The many faces of diabetes in American youth: type 1 and type 2 diabetes in five race and ethnic populations: the SEARCH for Diabetes in Youth Study. Diabetes Care. 2009; 32(Suppl 2):S99–101. [PubMed: 19246580]
7. Diamond Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990–1999. Diabet Med. 2006; 23:857–66. [PubMed: 16911623]
8. Shapira Y, Agmon-Levin N, Shoenfeld Y. Defining and analyzing geoepidemiology and human autoimmunity. J Autoimmun. 2010; 34(3):J168–77. [PubMed: 20034761]
9. MacFarlane AJ, Strom A, Scott FW. Epigenetics: deciphering how environmental factors may modify autoimmune type 1 diabetes. Mamm Genome. 2009; 20(9–10):624–32. [PubMed: 19697079]
10. Fourlanos S, Varney MD, Tait BD, Morahan G, Honeyman MC, Colman PG, et al. The Rising Incidence of Type 1 Diabetes is Accounted for by Cases with Lower-Risk Human Leukocyte Antigen Genotypes. Diabetes Care. 2008; 31(8):1546–9. [PubMed: 18487476]
11. Harrison LC, Honeyman MC, Morahan G, Wentworth JM, Elkassaby S, Colman PG, et al. Type 1 diabetes: Lessons for other autoimmune diseases? J Autoimmun. 2008; 31(3):306–10. [PubMed: 18558477]
12. Borchers AT, Uibo R, Gershwin ME. The geoepidemiology of type 1 diabetes. Autoimmun Rev. 2010; 9(5):A355–65. [PubMed: 19969107]
13. Roivainen M, Klingel K. Virus Infections and Type 1 Diabetes Risk. Curr Diab Rep. 2010 Oct; 10(5):350–6. [PubMed: 20680525]
14. Round JL, O'Connell RM, Mazmanian SK. Coordination of tolerogenic immune responses by the commensal microbiota. J Autoimmun. 2010; 34(3):J220–5. [PubMed: 19963349]
15. Neu J, Lorca G, Kingma SDK, Triplett EW. The Intestinal Microbiome: Relationship to Type 1 Diabetes. Endocrinol Metab Clin N Am. 2010; 39(3):563–71.
16. Ziegler AG, Pflueger M, Winkler C, Achenbach P, Akolkar B, Krischer JP, et al. Accelerated progression from islet autoimmunity to diabetes is causing the escalating incidence of type 1 diabetes in young children. J Autoimm. 2011 Mar 2. [Epub ahead of print].
17. Todd JA. Etiology of Type 1 Diabetes. Immunity. 2010; 32(4):457–67. [PubMed: 20412756]
18. Eschler DC, Hasham A, Tomer Y. Cutting Edge: The Etiology of Autoimmune Thyroid Diseases. Clin Rev Allerg Immunol. 2011 Jan 14. [Epub ahead of print].

19. Hewagama A, Richardson B. The genetics and epigenetics of autoimmune diseases. J Autoimmun. 2009; 33(1):3–11. [PubMed: 19349147]