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Editorial

Juvenile diabetes

What was termed juvenile diabetes is now referred to as type 1 diabetes with the recognition that the disease can occur at any age. The American Diabetes Association aetiologic classification distinguishes type 1A (autoimmune) from type 1B (non-autoimmune). Characteristic of type 1A diabetes is the presence of one or more islet autoantibodies reacting with GAD65 (glutamate decarboxylase), insulin, IA-2 (insulinoma antigen-2) and/or ZnT8 (zinc transporter 8). The most common form of childhood onset diabetes in Western societies is type 1A but as many as one half of Hispanic, African American and Asian children developing diabetes in the U.S., have other forms of diabetes (lacking islet autoantibodies) including a ketosis prone form with intermittent remissions (type 1.5).

Two major forms of diabetes pathology are distinguished by the presence or absence of pseudoatrophic islets (Pattern A: with all or a subset of islets lacking all insulin secreting beta cells usually in a lobular pattern; Pattern B: islets with decreased beta cells per islet but all islets with some beta cells)[1]. Pattern A appears to be a pathologic *sine qua non* of type 1A diabetes although there are rare disorders that can also lead to pseudoatrophic islets [*e.g.* Wolfram's syndrome - DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness)]. Pancreas from patients with type 2 diabetes and likely ketosis prone diabetes (type 1.5) have pattern B. Investigators throughout the world can view and manipulate scanned slides of pancreas from patients with diabetes with these patterns through the web after they register with the nPOD program headed by Dr Mark Atkinson *(www.jdrfnpod.org)*.

If beta cells are present in a patient with type 1A diabetes, their distribution is usually lobular and the islets hyper-express class I HLA molecules. This hyper-expression is an enigma in that all cells of the islets (including glucagon cells) have increased class I expression, even in islets where there is no apparent T cell infiltration. Once a type 1A patient's beta cells are entirely destroyed, the islets no longer hyper-express HLA class I. This hyper-expression of class I is likely a clue to pathogenesis as it is not found in pancreas from patients with other forms of diabetes.

Amongst children developing diabetes who lack anti-islet autoantibodies, approximately 10 per cent have defined monogenic diabetes disorders. In Asian countries a form of "fulminant" diabetes has been described, which is usually characterized by a complete loss of C-peptide and near normal HbA_1c at onset[2]. Although this form of diabetes also lacks islet autoantibodies, HLA alleles associated with Asian type 1A diabetes are present[2] suggesting that it is a very rapid autoimmune variant where perhaps there has not been sufficient time to develop islet autoantibodies.

One can divide the development of type 1A diabetes into a series of stages beginning with genetic susceptibility[3]. Most of the loci (>50 genetic loci confirmed) are presumed to influence maintenance of tolerance[4]. Despite the large number of loci, only three have appreciable odds ratios, the major histocompatibility complex (MHC), the insulin gene and a molecule influencing T cell receptor signaling, PTPN22. The MHC is the major determinant of risk for type 1A diabetes. The highest risk genotype is DR3-DQB1*0201/DR4-DQB1*0302 and there are protective alleles such as DR15-DQA*0102/DQB1*0602. DR3/4 heterozygous siblings of a patient with diabetes have a risk of developing diabetes >25 per cent. The primary targets of islet autoimmunity are believed to be insulin and proinsulin[5]. Of note, the insulin gene polymorphism associated with protection from type 1A diabetes is associated with greater expression of insulin within the thymus[6]. Type 1A diabetes is

associated with multiple autoimmune disorders and even at diabetes onset approximately a third of patients have other autoimmune manifestations[7]. Thyroid autoimmunity is most common, but 1.5 per cent of patients with type 1A diabetes express 21-hydroxylase autoantibodies predictive of Addison's disease and simple annual monitoring of ACTH in 21-hydroxylase antibody positive patients allows early detection of adrenal dysfunction which should lead to formal testing of stimulated cortisol secretion. Celiac disease is also relatively common in patients with type 1A diabetes (primarily related to shared HLA susceptibility alleles[8]) and screening of transglutaminase autoantibodies allows detection of "asymptomatic" disease[8].

Given that type 1A diabetes is an autoimmune disease that almost always develops slowly we can now predict not only risk of diabetes (presence of ≥2 biochemical autoantibodies)[9] but potentially the rate of disease progression (correlates with levels of insulin autoantibodies) and approximate age of onset[10]. It is likely that autoantibodies primarily reflect the activity of autoimmune T lymphocytes that ultimately destroy beta cells. The biochemical assays for islet autoantibodies also aid in diagnosis of type 1A, especially amongst adults clinically diagnosed with type 2 diabetes, and young children lacking islet autoantibodies. A subset of monogenic diabetes can be treated with oral hypoglycaemic agents.

Environmental factors triggering human diabetes are not yet well defined. A rat model with diabetes susceptible MHC (Kilham virus) may reflect viral pathogenesis in man. In this model the virus does not infect the islets but activates innate immunity followed by specific T cell targeting of beta cells[11].

At present, we cannot safely prevent the development of type 1A diabetes. A number of immunosuppressive and immunomodulatory therapies (anti-CD20, CTLA4-Ig, anti-CD3) can delay loss of C-peptide (a measure of insulin secretion and indirectly beta cell mass) but only for approximately 6 months[12]. Antigen specific therapies have not delayed loss of C-peptide after diabetes onset. In an analysis of the subset of DPT-1 trial participants with high levels of insulin autoantibodies, oral insulin (to induce mucosal tolerance) appeared to delay progression to diabetes[12] and repeat Trialnet study is underway to test this intriguing possibility.

We suggest that more specifically targeted therapies need to be developed such as methods to administer or expand regulatory T cells targeting islet molecules or therapies that target autoreactive T cell trimolecular recognition complexes[13]. This complex consists of presenting MHC molecule, specific peptide in an appropriate register for recognition, and autoreactive T cell receptor. One approach to target T cell antigen recognition is the development of small molecules targeting binding pockets of MHC alleles associated with type 1 diabetes[14]. Another monoclonal approach utilizes antibodies directed at specific T cell receptor elements[15].

As diabetes care improves, the bar for considering immunotherapy for type 1A diabetes is fortunately being raised, although most of the technologies are expensive. In particular, insulin analogues allow basal and bolus regimens that can achieve glycaemic control similar to patients using insulin pumps. Both faster acting (injection for bolus) and longer acting insulin (for basal) are under development. Continuous glucose monitors[16], including those that can turn off an insulin pump if hypoglycaemia is detected are now clinically approved in several countries. The results of human islet transplantation have improved but allo-transplantation is limited by the need for immunosuppression[17]. The reversal of hyperglycaemia with islet transplantation can be very dramatic and can last years. Severe hypoglycaemia is totally prevented. Continuous glucose monitoring devices are likely to decrease consideration of islet transplantation unless islet transplantation without immunosuppression can be achieved and the procedure simplified[17]. Transplanting islets from stem cells will likely face similar barriers to that of islet transplantation. Both transplant immunity and autoimmunity are able to target transplanted islet cells years after diabetes onset[18].

There are important gaps in our understanding of type 1 diabetes and more important gaps in our therapeutic options. With the ability to predict the disease, the lack of effective and safe preventive therapy is an obvious major concern. The technology for measuring islet autoantibodies has progressed rapidly and multiple non-radioactive assays are now available that would allow general population screening if a preventive therapy was available[19]. Related to the prior probability of type 1A diabetes, a single islet autoantibody minimally increases risk of diabetes. It is the presence of ≥2 of the four major islet autoantibodies (individual assays with 99% specificity reacting with GAD65, insulin, IA-2, or ZnT8) that predicts onset. Programmes such as nPOD studying general population cadaveric donors indicate that between

1/300 and 1/1000 cadaveric donors express multiple biochemical islet autoantibodies, even though such programmes mostly screen older donors. Thus in the U.S. alone there may be more than 500,000 individuals developing type 1A diabetes. Concordant with the scope of the problem (type 1A diabetes is doubling in most developed countries every 20 years[20]) a major effort is underway to develop immunologic preventive therapies. With patients willing to participate in trials of prevention given only partially effective therapy and multiple animal models where disease can be prevented, it is our hope that this effort will result in general algorithms to diagnose pre-type 1 diabetes and prevent it.

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References

1. Gianani R, Campbell-Thompson M, Sarkar SA, Wasserfall C, Pugliese A, Solis JM, *et al*. Dimorphic histopathology of long-standing childhood-onset diabetes. *Diabetologia* 2010; *53* : 690-8.
2. Kawabata Y, Ikegami H, Awata T, Imagawa A, Maruyama T, Kawasaki E, *et al*. Differential association of HLA with three subtypes of type 1 diabetes: fulminant, slowly progressive and acute-onset. *Diabetologia* 2009; *52* : 2513-21.
3. Eisenbarth GS. Banting Lecture 2009: An unfinished journey: molecular pathogenesis to prevention of type 1A diabetes. *Diabetes* 2010; *59* : 759-74.
4. Concannon P, Rich SS, Nepom GT. Genetics of type 1A diabetes. *N Engl J Med* 2009; *360* : 1646-54.
5. Nakayama M, Abiru N, Moriyama H, Babaya N, Liu E, Miao D, *et al*. Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice. *Nature* 2005; *435* : 220-3.
6. Pugliese A, Zeller M, Fernandez A Jr, Zaliberg LJ, Bartlett RJ, Ricordi C, *et al*. The insulin gene is transcribed in the human thymus and transcription levels correlated with allelic variation in the INS VNTR-IDDM2 susceptibility locus for type 1 diabetes. *Nat Genet* 1997; *15* : 293-7.
7. Triolo TM, Armstrong TK, McFann K, Yu L, Rewers MJ, Klingensmith GJ, *et al*. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care* 2011; *34* : 1211-3.
8. Liu E, Li M, Emery LL, Taki l, Barriga K, Tiberti C, *et al*. Natural history of antibodies to deamidated gliadin peptides and transglutaminase in early childhood celiac disease. *J Pediatr Gastroenterol Nutr* 2007; *45* : 293-300.
9. Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Jackson RA, Chase HP, *et al*. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. *Diabetes* 1996; *45* : 926-33.
10. Steck AK, Johnson K, Barriga KJ, Miao D, Yu L, Hutton JC, *et al*. Age of islet autoantibody appearance and mean levels of insulin, but not GAD or IA-2 autoantibodies, predict age of diagnosis of type 1 diabetes: diabetes autoimmunity study in the young. *Diabetes Care* 2011; *34* : 1397-9.
11. Zipris D, Lien E, Nair A, Xie JX, Greiner DL, Mordes JP, *et al*. TLR9-signaling pathways are involved in Kilham rat virus-induced autoimmune diabetes in the biobreeding diabetes-resistant rat. *J Immunol* 2007; *178* : 693-701.
12. Skyler JS, Ricordi C. Stopping type 1 diabetes: Attempts to prevent or cure type 1 diabetes in man. *Diabetes* 2011; *60* : 1-8.
13. Kobayashi M, Jasinski J, Liu E, Li M, Miao D, Zhang L, *et al*. Conserved T cell receptor alpha-chain induces insulin autoantibodies. *Proc Natl Acad Sci USA* 2008; *105* : 10090-4.
14. Michels AW, Ostrov DA, Zhang L, Nakayama M, Fuse M, McDaniel K, *et al*. Structure-based selection of small molecules to alter allele-specific MHC class II antigen presentation. *J Immunol* 2011; *187* : 5921-30.
15. Mordes JP, Cort L, Norowski E, Leif J, Fuller JM, Lernmark A, *et al*. Analysis of the rat Iddm14 diabetes susceptibility locus in multiple rat strains: identification of a susceptibility haplotype in the Tcrb-V locus. *Mamm Genome* 2009; *20* : 162-9.
16. Wadwa RP, Fiallo-Scharer R, Vanderwel B, Messer LH, Cobry E, Chase HP. Continuous glucose monitoring in youth with type 1 diabetes. *Diabetes Technol Ther* 2009; *11* (Suppl 1): S83-91.
17. Gill RG, Bishop NH. Clinical islet transplantation: where immunity and metabolism intersect? *Curr Opin Endocrinol Diabetes Obes* 2012; *19* : 249-54.
18. Sutherland DE, Sibley R, Xu XZ, Michael A, Srikanta AM, Taub F, *et al*. Twin-to-twin pancreas transplantation: reversal and reenactment of the pathogenesis of type I diabetes. *Trans Assoc Am Physicians* 1984; *97* : 80-7.
19. Yu L, Miao D, Scrimgeour L, Johnson K, Rewers M, Eisenbarth GS. Distinguishing persistent insulin autoantibodies with differential risk: nonradioactive bivalent proinsulin/insulin autoantibody assay. *Diabetes* 2012; *61* : 179-86.
20. Forlenza GP, Rewers M. The epidemic of type 1 diabetes: what is it telling us? *Curr Opin Endocrinol Diabetes Obes* 2011; *18* : 248-51.