Is Diabetes Mellitus a Continuous Spectrum?

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BACKGROUND: Diabetes mellitus has been historically divided into type 1 and type 2 diabetes, with type 1 being an autoimmune disease and type 2 being primarily a metabolic disease.

CONTENT: The current diabetes classification scheme needs to be reevaluated because of the accumulating evidence of immune system involvement in the physiopathology of type 2 diabetes.

SUMMARY: There are similarities and differences between type 1 and type 2 diabetes with regard to pathogenesis, pathophysiology, and genetics. We propose a resolution to the dilemma of the current classification scheme.

Historically, diabetes mellitus has been classified into 2 clinical types: type 1 diabetes (T1D)3 and type 2 diabetes (T2D) (1, 2). The diagnosis of T1D vs T2D is usually made on the basis of such criteria as age at onset, abruptness of hyperglycemic symptoms, presence of ketosis, degree of obesity, and perceived need for insulin replacement. T1D patients were historically defined by diagnosis in childhood or young adulthood (before the age of 35 years). In contrast, T2D was believed to occur primarily in adults and has historically been considered nonautoimmune in nature. The age distinction between the 2 diseases has proved to be problematic, however, with the identification of “pediatric type 2 diabetes patients” (3–5), “adult type 1” diabetes patients (6), and patients demonstrating characteristics of both T1D and T2D, leading some researchers to coin the terms “type 1.5 diabetes” and “double diabetes” (7–9). In recent years, many notable discoveries have made further assaults on the current scheme of diabetes classification. Evidence to support the concept of immune system involvement in T2D, with both similarities to and differences from the pathogenesis of T1D, is accumulating (10, 11). In this review, we discuss some of these similarities and differences between T1D and T2D and then propose our resolution to the current classification dilemma.

Pathogenesis

In the pancreas of T1D patients, the immune system selectively destroys β cells in a process known as insulitis (12). Recently, immune cells have also been demonstrated to infiltrate the pancreatea of T2D patients (10–14). In T1D, an autoimmune reaction characterizes the insulitis, whereas a more “autoinflammatory” infiltrate appears to characterize the insulitis associated with T2D (10–14). Moreover, islet-reactive T cells responding to multiple islet proteins have been found in both T1D patients (15–18) and phenotypic T2D patients with and without islet autoantibodies, the historical hallmark of islet autoimmunity (19–22). Potential differences between T1D patients and autoimmune phenotypic T2D patients in the islet proteins recognized by T cells have been identified, hinting at potentially different pathogenic mechanisms (21). These studies suggest that T-cell–mediated islet damage may be a component of more than just classic T1D. Recently, we demonstrated in phenotypic T2D patients that the presence of islet-reactive T cells identified patients with a more severe β-cell lesion, compared with assessing islet autoantibodies alone (23). This result thus indicated a potential link between the presence of islet-reactive T cells in T2D patients and β-cell destruction.

Islet autoantibodies have historically been relied upon as indicators of the presence of islet autoimmunity in diabetes patients. The most common islet autoantibodies, which are islet cell autoantibodies (ICAs), glutamic acid decarboxylase (GAD) autoantibodies, insulinoma-associated antigen 2 (IA-2) autoantibodies, and insulin autoantibodies, are found in childhood T1D patients, and many of these patients demonstrate positivity for multiple islet autoantibodies. In fact, positivity for an increasing number of islet autoantibodies is associated with a progressively greater risk of developing T1D (24–28). In contrast, singular positivity for either ICAs or GAD autoantibodies is characteristic of autoimmune T2D patients (9, 19, 20, 29).
typic T2D patients, GAD autoantibodies and ICAs are much more common than insulin, IA-2, and zinc transporter 8 (ZnT8) autoantibodies (8, 9, 29, 30). IA-2 autoantibodies, however, are more common in Japanese autoimmune T2D patients (29). Wenzlau et al. (31) detected ZnT8 autoantibodies in up to 80% of new-onset T1D patients, compared with <2% of controls, <3% of T2D patients, and up to 20% of patients with other autoimmune diseases. Because the islet autoantibodies used to categorize and identify T2D patients are islet autoantibodies that were originally identified in T1D patients, there may be other islet autoantibodies specific to autoimmunity in phenotypic T2D that have not yet been identified. Such antibodies might classify such patients more accurately or differently. In support of this concept, Seissler et al. (32) demonstrated that GAD and IA-2 autoantibodies could block ICA staining in approximately 60% of sera from T1D patients but in a much lower percentage of sera from autoimmune T2D patients.

Pathophysiology

A greater rate of decline in C-peptide has been reported in adult T1D patients than in adult T2D patients (29, 33, 34); differences between T1D and T2D patients in insulin secretion have also been reported (35). Increased body weight, central obesity, hypertension, and dyslipidemia are indicative of the metabolic syndrome that has been associated with both T1D and T2D (36, 37). Insulin resistance, an integral part of the pathophysiology of T2D, is affected by many variables, including age, body mass index, ethnicity, physical activity, and medications. When insulin resistance is assessed by the homeostasis model and corrected for body mass index, autoimmune and nonautoimmune T2D patients show no difference in insulin resistance (38). Insulin resistance has also been recognized in T1D and is associated with progression to disease in people at risk for T1D (39–42). Interleukin-1β has been hypothesized to be both a component in the development of insulin resistance and the driving force in disease development, for both T1D and T2D (10–13, 43–45). In fact, interleukin-1β is increased in the circulation and the pancreatic islets during progression from obesity to T2D (45) and is a proinflammatory cytokine acting during the autoimmune process of T1D (43, 44). The improvement in T2D patients observed with the administration of an interleukin-1 receptor antagonist (46) further emphasizes the importance of understanding the immune components in the development of T1D and T2D so that potential treatment targets may be identified.

Genetics

On the genetics front, there are similarities and differences between autoimmune T1D and T2D patients, as well as differences between autoimmune and nonautoimmune T2D patients. The HLA-DR2 and DQB1*0602 phenotype that has been associated with protection against childhood T1D does not appear to confer protection against adult autoimmune T2D (37). Compared with nonautoimmune T2D patients, autoimmune T2D patients are reportedly more commonly positive for HLA-DR3 and -DR4 and their associated DQB1 alleles 0201 and 0302, which are haplotypes strongly linked to a predisposition to childhood T1D (29, 30, 47). Other non-HLA genetic differences between T1D and T2D are seen in the MICA4 (MHC class I polypeptide-related sequence A) gene (48, 49) and an allelic polymorphism within the promoter region of the TNF (tumor necrosis factor) gene (the TNF2 allele) (50). Recent genomewide association studies have demonstrated a link between the polymorphisms in the SLC30A10 (solute carrier family 30, member 10) gene and T2D, although ZnT8 autoantibodies are rarely detected in phenotypic T2D (51–53) but are common in T1D patients. A family history of diabetes has been identified for both T1D and T2D as a risk factor for the development of diabetes (54), with the risk of developing diabetes increasing with the number of affected relatives (54–56). Therefore, differences at the genetic level may help account for not only the differences seen in pathogenic mechanisms but also similarities that may drive the development of the diabetes disease process.

Proposal and Conclusions

We propose that diabetes mellitus encompasses a spectrum of diseases with immune system involvement. At one end of the spectrum are patients with classic childhood T1D encompassing autoimmune-mediated destruction of β cells. At the other end of the spectrum is age-related deterioration of glucose tolerance. In the middle is T1D with a disease onset in early adulthood (twenties and thirties), followed by autoimmune phenotypic T2D patients and nonimmune phenotypic T2D patients (Fig. 1). The differences between T1D and T2D patients in autoimmune and T-cell recognition of islet proteins suggest important differences between the 2 diabetes subgroups in the disease process;
however, the results of immune system involvement in β-cell destruction may be similar. The observed similarities and differences in etiologies and the prevalences of the subgroups along the spectrum of diabetes disease are areas of much-needed research. We propose that the schema for separating patients into T1D and T2D on the basis of phenotypic characteristics be discarded and that a new framework that encompasses the spectrum of diabetes disease be used instead. We recommend that the new disease distinctions be based on immune system involvement in the destruction of β cells. As efficacious and safe treatments that block the deleterious effects of the immune system on pancreatic β cells become available, the use of such agents will dramatically change how providers treat patients with diabetes.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References


