Latent Autoimmune Diabetes in Adults

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Context: Autoantibodies that are reactive to islet antigens are present at the time of diagnosis in most patients with type 1 diabetes. Additionally, approximately 10% of phenotypic type 2 diabetic patients are positive for at least one of the islet autoantibodies, and this group is often referred to as "latent autoimmune diabetes in adults (LADA)." These patients share many genetic and immunological similarities with type 1 diabetes, suggesting that LADA, like type 1 diabetes, is an autoimmune disease. However, there are differences in autoantibody clustering, T cell reactivity, and genetic susceptibility and protection between type 1 diabetes and LADA, implying important differences in the underlying disease processes.

Evidence Acquisition and Synthesis: In this clinical review, we will summarize the current understanding of LADA based on the MEDLINE search of all peer-reviewed publications (original articles and reviews) on this topic between 1974 and 2009.

Conclusions: In LADA, diabetes occurs earlier in the β-cell-destructive process because of the greater insulin resistance. Complexities arise also because of variable definitions of LADA and type 1 diabetes in adults. As immunomodulatory therapies that slow or halt the type 1 diabetes disease process are discovered, testing these therapies in LADA will be essential. (***J Clin Endocrinol Metab*** **94: 4635–4644, 2009)**

In clinical practice, the diagnosis of type 1 and type 2 diabetes is made using phenotypic characteristics such as age at onset, abruptness of onset of hyperglycemia, ketosis-proneness, degree of obesity (specifically central and intraabdominal), prevalence of other autoimmune diseases, and need for insulin replacement therapy. However, this clinical distinction is not always perfect (1, 2). The presence of genetic (3), immunological (4), and functional complexities (5) limits our ability to distinguish the type 1 *vs.* the type 2 disease processes. The disease process in classic type 1 patients is believed to be autoimmune in nature, whereas the disease process in classic type 2 is not autoimmune (6–8). However, there is increasing clinical evidence that highlights significant overlap between type 1 and type 2 diabetes, and the classification of diabetes into two main types has been challenged.

Discovery of islet cell antibodies in 1974 in the sera of subjects with type 1 diabetes provided very strong evidence that the β-cell lesion of type 1 diabetes was autoimmune in nature (9, 10); autoimmune β-cell dysfunction and destruction leads to insulin deficiency and generation of autoantibodies in the circulation, such as autoantibodies to islet-cell cytoplasm (ICA), and/or to glutamic acid decarboxylase 65 (GAD65; anti-GAD), and/or to the intracytoplasmatic domain of the tyrosine phosphatase-like protein IA-2 (IA-2A). Because there are no reliable markers for type 2 diabetes, absence of markers and/or manifestations of type 1 diabetes is often taken as indicating type 2 diabetes.

It was demonstrated by Irvine *et al.* (11) that about 11% of subjects with type 2 diabetes were also positive for ICAs. Compared with ICA-negative (ICA^-) type 2 diabetes, this ICA-positive (ICA^+) subset of type 2 diabetes subjects tended to fail sulfonylurea therapy and needed insulin treatment earlier (11). Similar subsets of phenotypic type 2 diabetes subjects who are positive for the antibodies

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-1120 Received June 11, 2009. Accepted September 9, 2009.
First Published Online October 16, 2009

Abbreviations: BMI, Body mass index; GAD, glutamic acid decarboxylase; HLA, histocompatibility leukocyte antigen; IAA, insulin autoantibodies; ICA, islet-cell cytoplasm; LADA, latent autoimmune diabetes of adults; ZnT8, zinc transporter.

commonly found in type 1 diabetes have been demonstrated by several investigators. Zimmet (12) introduced the term "latent autoimmune diabetes of adults" (LADA) to describe this subgroup of adult phenotypic type 2 diabetes patients positive for an autoantibody to GAD (which implies the presence of autoimmunity and immune-mediated β-cell dysfunction and damage as part of their disease process) and who present clinically without ketoacidosis and weight loss. As expected for an immune attack on the β-cells, these patients also became insulin dependent more rapidly than "classic" type 2 diabetes patients who were negative for islet autoantibodies (12). Autoantibody-positive phenotypic type 2 diabetes patients or LADA have also been labeled as slowly progressive type 1 diabetes (13, 14), latent type 1 diabetes (15, 16), double diabetes (17), and type 1.5 diabetes (16, 18–20).

Definition, Demographic, and Clinical Characteristics

Epidemiological studies suggest that LADA may account for 2–12% of all cases of diabetes (12, 14, 18, 21–24). The typical LADA patient is generally older than 35 yr and nonobese, and diabetes is controlled initially with diet; however, within a short period (months to years), dietary control fails, requiring oral agents and progression to insulin dependency. The progression to insulin dependence in LADA patients is believed to be more rapid than in antibody-negative, obese type 2 diabetes subjects. The eventual clinical features of these patients include weight loss, ketosis proneness, unstable blood glucose levels, and an extremely diminished C-peptide reserve (14).

We do not know whether autoimmune diabetes in adults is due to the same underlying disease process as childhood type 1 diabetes (16), and phenotypically one can see at least three separate populations of autoimmune diabetes in adults: LADA, adult onset type 1 diabetes, and obese patients with phenotypic type 2 diabetes who are antibody positive (type 1.5) (16). In an attempt to standardize the definition of LADA, the Immunology of Diabetes Society has recently proposed the following criteria: patients should be at least 30 yr of age, positive for at least one of the four antibodies commonly found in type 1 diabetic patients (ICAs and autoantibodies to GAD65, IA-2, and insulin), and not treated with insulin within the first 6 months after diagnosis. Although the latter requirement is subjective, it is meant to distinguish LADA and type 1 diabetes occurring in patients more than 30 yr of age (25, 26). However, similar pathophysiology also occurs in obese children who are non-ketosis-prone but who have autoantibodies characteristic of type 1 diabetes (27–29). These patients do not have a specific name like LADA, but defining LADA by the age criteria of older than 30 yr may be arbitrary and incorrect.

Recently, it has been observed that the LADA patients share genetic features with both type 1 and type 2 diabetes (17). The role of obesity and the degree of insulin resistance in LADA are other areas of controversy. Normal β-cells compensate for insulin resistance by secreting more insulin, and the product of insulin sensitivity and insulin secretion ("disposition index") is normally a constant (30). Patients with insulin resistance will demonstrate hyperglycemia with a lesser degree of absolute insulin deficiency compared with subjects who are insulin-sensitive. Because LADA subjects span the spectrum from lean to obese, differences in insulin sensitivity could be an important variable in their physiology.

Humoral Immune Response

Antibody positivity and clustering

The presence of autoantibodies along with islet-reactive T cells in both LADA and classic childhood type 1 diabetes provides strong evidence that the underlying disease process in both patient groups is autoimmune. However, there are differences in antibodies between LADA and type 1 diabetes. All four well-described type 1 diabetes-associated islet autoantibodies—ICAs, anti-GAD, IA-2A, and insulin autoantibodies (IAA)—and the more recently identified zinc transporter (ZnT8) antibody are common in childhood type 1 diabetes; many type 1 diabetes patients are also positive for multiple autoantibodies (31). Thus, antibody clustering is a characteristic feature of classic childhood type 1 diabetes. Many researchers have demonstrated that anti-GAD and ICA are much more common than IAA, IA-2A, and ZnT8 antibodies in LADA patients *vs.* type 1 patients (17, 18, 31–34). Wenzlau *et al.* (31) reported that ZnT8 autoantibodies were detected in up to 80% of new-onset type 1 diabetes subjects compared with less than 2% of controls, less than 3% of type 2 diabetes patients, and up to 20% of patients with other autoimmune diseases. By definition, the presence or absence of autoantibodies distinguishes between patients with "classic" nonautoimmune type 2 diabetes and LADA (25). In our study of 125 adult phenotypic type 2 patients screened for autoantibodies, 36 (28.8%) patients were positive for at least one autoantibody (Fig. 1) (18).

In nondiabetic relatives of patients with type 1 diabetes, risk of future type 1 diabetes is directly proportional to the number of positive autoantibodies (35–37). Positivity for only one autoantibody (ICA or anti-GAD) is characteristic

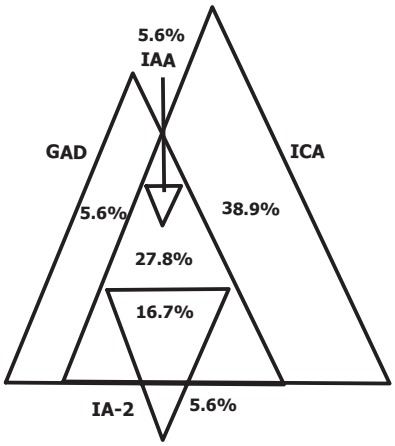

FIG. 1. Clustering of autoantibodies in autoantibody-positive patients. Numbers (%) refer to the percentage of the antibody-positive patients who were positive for the respective antibodies. [Reproduced with permission from R. Juneja *et al.*: *Metabolism* 50: 1008–1013, 2001 (18).]

of LADA patients (18, 20, 33, 38–41). Recent studies have reported that the clinical characteristics of LADA patients correlate with the titer and numbers of diabetes-associated autoantibodies (42–44). Simultaneous presence of multiple autoantibodies and/or a high titer of anti-GAD autoantibodies, compared with single and low-titer autoantibody, was associated with an earlier age at onset, lower fasting C-peptide values, and a higher likelihood for future insulin requirement (44, 45).

Antigenic differences between LADA and type 1 diabetes

GAD and IA-2 could block ICA staining in approximately 60% of sera from type 1 diabetes subjects but only in 37.5% of sera from people with LADA, suggesting that autoantibodies to antigens other than GAD and IA-2 are more prevalent in LADA (46). The IgG4 subclass of anti-GAD has been demonstrated to be more frequent in LADA than in type 1 diabetes, implying a more "regulated" immune response (a dominant TH2 immune response) in LADA (47). We identified possible differences in epitope specificity of anti-GAD in LADA *vs.* type 1 diabetes using recombinant ^{35}S-GAD65/67 fusion proteins (48). More than 90% of type 1 diabetes patients' sera bound to the middle or COOH-terminal portion of GAD65; similar binding was seen in only 65% of sera from LADA patients. In contrast, the NH_2-terminal portion of GAD65 was recognized by 20% of LADA patients compared with 5% of type 1 diabetic patients (48). Similar results using GAD65-specific recombinant Fabs have also been found in our recent studies (49). The United Kingdom Prospective Diabetes Study (UKPDS) has shown that although GAD autoantibodies persisted for 5 yr after diagnosis of LADA, some GAD autoantibodies are reactive to different GAD65 epitopes compared with type 1 diabetes and are not associated with disease progression or future insulin requirements (50). A recent Italian study has demonstrated that autoantibody reactivity to IA-2 in LADA patients may well be much more frequent than so far reported if a particular IA-2 (256-760) construct is used, and this can be considered as a new, sensitive, and novel diagnostic tool for the detection of islet autoimmunity in subjects with type 2 diabetes (51).

T Cell Studies

T cell responses to islet proteins in type 1 diabetes and LADA

T cell assays to measure reactivity to islet antigens in human type 1 diabetes have been developed over the last several years; one such assay, called cellular immunoblotting assay and developed by our group, uses proteins from human islets separated into 18 different molecular weight regions using SDS-PAGE. Excellent sensitivity and specificity for differentiating type 1 diabetes from controls was demonstrated by this assay in a masked National Institutes of Health—Immune Tolerance Network Workshop (52). Similar results were demonstrated in a subsequent masked TrialNet workshop (53).

T cells responding to multiple islet proteins have been found in LADA patients with and without autoantibodies (38, 39, 54, 55), in type 1 diabetes patients (56–61), and in subjects at risk of developing type 1 diabetes before development of clinical disease (57). Using the cellular immunoblotting assay, we have identified differences in islet proteins recognized by T cells from type 1 *vs.* LADA (54). As illustrated in Fig. 2, there are some islet proteins that T cells from both type 1 diabetes and LADA subjects appear to respond to equally (molecular mass, 116, 97, and 60 kDa). However, there are also molecular mass regions that may differentiate T cell responses from type 1 diabetes *vs.* LADA (proteins in the molecular mass regions 65–90 and 21–38 kDa). It is not yet understood which immunological mechanisms are important in the delay and apparent differences in the pathogenesis of LADA *vs.* type 1 diabetes. Many of the above findings point to potential differences in immunological regulatory mechanisms.

T cell responses to islets in type 2 diabetes and LADA

We have recently identified a group of phenotypic type 2 diabetes subjects who have T cells reactive to islet proteins but are negative for islet autoantibodies (55). We have termed this group of patients as T-LADA. Thus, as-

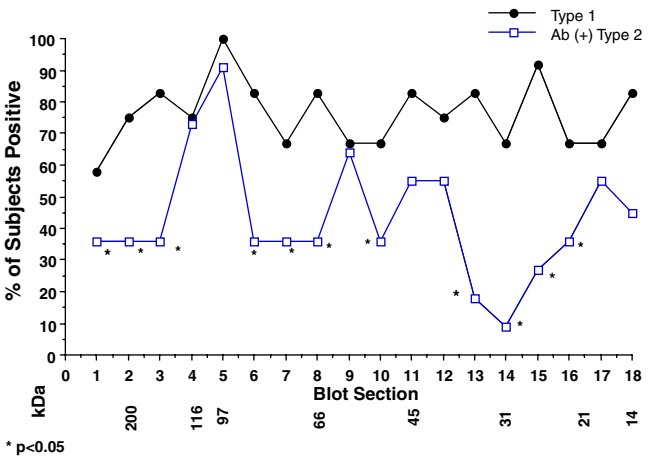

FIG. 2. T cell responses of 12 type 1 diabetes patients (*closed circles*) and 11 autoantibody-positive type 2 patients (type 1.5 patients; *open squares*). The percentage of subjects responding to each molecular mass region is shown. A positive response is taken as SI >2.0. Blot sections correspond to molecular mass regions >200 kDa (1) and <14 kDa (18). *, $P < 0.05$ indicates significant difference. [Reproduced with permission from B. M. Brooks-Worrell *et al.*: *Diabetes* 48:983–988, 1999 (54).]

sessing patients for T cell responses to islet proteins may help distinguish LADA from type 2 diabetes, especially if the LADA subjects are autoantibody negative. With the identification of T-LADA, the use of only autoantibodies to screen phenotypic type 2 diabetes subjects for autoimmune diabetes may need to be reevaluated (55). Recently, we observed the importance of assessing T cell responses from type 2 diabetes subjects to islet proteins by demonstrating that identifying subjects with type 2 diabetes with T cells responsive to islet proteins identified those with a more severe β-cell lesion compared with assessing islet autoantibodies alone (62).

Other T cell studies

In health, immunological tolerance is maintained by multiple central and peripheral mechanisms including the action of a specialized set of regulatory T cells characterized by expression of CD4 and CD25 (CD4+CD25+FOXP3+ Treg). It has been suggested that a defect in this cell population, either numerically or functionally, could contribute to the development of autoimmune diseases, such as type 1 diabetes (63). Yang *et al.* (64) in their study of lymphocyte subsets showed that $CD4^+$ regulatory T cells are reduced and the expression of FOXP3 mRNA in $CD4^+$ T cell was decreased in LADA patients.

Islet β-Cell Function, Insulin Resistance, and Islet Inflammation

β-Cell function

β-cell dysfunction in LADA has been reported to be intermediate between type 1 and type 2 diabetes (43, 65, 66). LADA subjects appear to have a faster decline in C-peptide levels compared with people with autoantibody negative type 2 diabetes (33, 43, 66). In comparison, a greater rate of decline in C-peptide has been reported in adult type 1 diabetes compared with LADA (33, 67). Other investigators have also observed differences in insulin secretion between type 1 diabetes, LADA, and type 2 diabetes. Gottsater *et al.* (67) found that the level of insulin secretion in LADA was intermediate between type 1 and type 2 diabetes and that fasting and stimulated C-peptide were reduced in LADA compared with type 2 diabetes.

Insulin resistance

The role of insulin resistance and its contribution to the pathophysiology of LADA is controversial; the degree of insulin resistance in LADA has been reported to be less than in type 2 diabetes and comparable to type 1 diabetes (68, 69). We have recently compared insulin resistance using the homeostasis model in LADA, antibody-negative type 2 diabetes, and normal control subjects correcting for the effect of body mass index (BMI) (26, 70). There was a positive correlation of BMI with insulin resistance in both LADA and type 2 diabetes, and insulin resistance was remarkably similar in both groups when corrected for BMI (70). Furthermore, subjects with both LADA and type 2 diabetes were more insulin resistant than normal control subjects when corrected for BMI. Some studies have reported a significantly lower mean BMI in LADA compared with patients with type 2 diabetes (69, 71), whereas other studies do not show a difference (70). However, the range of BMIs is often large, with tremendous overlaps between LADA and type 2 diabetes (18).

A recent study in adult European diabetes patients has shown that the prevalence of metabolic syndrome is significantly higher in type 2 diabetic patients than in patients with LADA or adults with type 1 diabetes (72); it was further shown that metabolic syndrome is not more prevalent in patients with autoimmune diabetes than in control subjects, and metabolic syndrome is not a characteristic of autoimmune diabetes (72).

Islet inflammation in type 1 and 2 diabetes

It is also becoming increasingly evident that many factors that are involved in the type 1 diabetes-specific process are also integral to the β-cell lesion in type 2 diabetes, including IL-1β, Fas, nuclear factor-κB, and increased expression of c-Myc (73, 74). Moreover, recent studies have also shown macrophage infiltration in islets of type 2 diabetes subjects (73, 74). The mechanisms leading to cytokine-induced β-cell dysfunction in type 1 diabetes and to nutrient-induced β-cell dysfunction in type 2 diabetes may

share common final pathways, including IL-1β signaling (73, 74). Thus, there seems to be a wide spectrum of associations between inflammatory reactions and the various diabetic syndromes. Type 1 diabetes is at one end of the spectrum for which there is convincing evidence that a chronic inflammation of the islets is an important feature of disease pathogenesis; at the opposite end of the spectrum is type 2 diabetes, which is clearly associated with systemic inflammation that could be either the cause or the consequence of some of the main features of the disease (75). Thus, one may hypothesize that classic type 1 and type 2 diabetes reflect two extremes of a continuum, connected by the central role of the failing β-cell (73). Finally, somewhere between these two extremes, one finds LADA, which seems to share some features of both extremes (75).

Genetic Susceptibility and Protection

Studies from both of the animal models (the NOD mouse and the BB rat) and human type 1 diabetes confirm the presence of strong genetic control over both susceptibility to and protection from diabetes. The greatest risk and protection is conferred by the major histocompatibility complex region, histocompatibility leukocyte antigen (HLA) in humans; however, other genes are also involved in the process.

HLA associations

It is well established that HLA DR3, DR4, and DQβ1*0201 and 0302 confer increased risk of type 1 diabetes. It is also known that other HLA alleles including DR2 and DQβ1*0301 and 0602 confer protection against type 1 diabetes. An increased frequency of HLA susceptibility alleles has been observed in LADA patients (20, 33, 34, 76, 77), but whether or not there are subtle differences between type 1 diabetes and LADA for specific alleles is controversial (20, 77, 78). The most consistent HLA-related finding is a relatively high frequency, compared with type 1 diabetes, of the protective alleles DR2 and DQβ1*0602 in subjects with LADA (79). The protection associated with DR2/DQβ1*0602 may partially explain the age of onset of LADA *vs.* childhood type 1 diabetes. A recent study compared a group of LADA subjects with control and adult type 1 diabetes (33). It was found that the HLA high-risk haplotype DR4-DQβ1*0302 and the DR3/DR4-DQβ1*0302 genotype were significantly more common in subjects with LADA compared with control subjects, whereas the frequencies were no different in LADA *vs.* adult onset type 1 diabetes (33). One could, thus, possibly hypothesize that the type 1 diabetes disease process is more aggressive, resulting in clinical presentation at a younger age in individuals with more susceptibility genes and less protective genes, and vice versa.

Non-HLA associations

Allelic variations at several non-HLA loci with increased risk for and protection from classic type 1 diabetes have also been investigated in subjects with LADA. An increased frequency of the cytotoxic T lymphocyte antigen-4 genotype A/G is seen in both type 1 diabetes and LADA, suggesting a similar role in both these types of diabetes (80). Similarly, allelic variation in the variable number of tandem repeats of the 5′ region of the insulin gene has been reported in both type 1 diabetes and LADA, but the relative risk associated with the 1S/S genotype was reported to be significantly stronger for LADA than for type 1 diabetes (81). Microsatellite polymorphism in the major histocompatibility complex class I chain-related gene A (MICA) has been associated with different autoimmune diseases including type 1 diabetes. MICA5 is associated with type 1 diabetes under the age of 25 yr, whereas MICA5.1 is associated with both LADA and type 1 diabetes over 25 yr of age (78, 82). Other associations reported include an allelic polymorphism within the promoter region of the TNF-α gene and a significantly lower frequency of TNF2 allele in LADA compared with type 1 diabetes or nondiabetic control subjects (83). Recent genome-wide association studies demonstrated a link between the ZnT8 gene polymorphisms and type 2 diabetes, although ZnT8 autoantibodies are rarely detected (84–90).

More recently, a single polymorphic Arg325 encoding residue polymorphism in *SLC30A8* has been shown to be associated with type 1 diabetes risk (91). Common variants in the TCF7L2 gene, in association with HLA-DQβ1 genotyping, can distinguish anti-GAD positive and anti-GAD negative diabetes subjects diagnosed between the ages of 15 and 34 yr (92). But, the TCF7L2 gene variants do not distinguish between autoimmune and nonautoimmune diabetes diagnosed between the ages of 40 and 59 yr, suggesting that the disease pathogenesis in middle-aged (40–59 yr) anti-GAD-positive subjects is different from young (15–34 yr) anti-GAD-positive diabetes subjects (92). Also, subjects with LADA share the same TCF7L2 genotype with type 2 diabetes (17). Thus, subjects with LADA appear to share genetic determinants common to both type 1 and 2 diabetes.

Significance of family history

Family history of diabetes has been identified as a risk factor for the development of diabetes, both type 1 and type 2 (25). Familial clustering of diabetes is believed in part to be due to a combination of shared genetic and environmental factors. For both type 1 and type 2 diabe-

tes, the risk of developing diabetes increases with an increasing number of affected relatives (92–94). Interesting recent reports have shown familial clustering of type 1 and type 2 diabetes genes and have suggested that selected susceptibility gene variants may be involved in the pathogenesis of type 1 and type 2 diabetes (73). The results of the Nord-Trøndelag Health Study (95) showed that family history of diabetes, although the type of diabetes in the relatives was unknown, was also a strong risk factor for the development of LADA.

Therapeutic Interventions

Knowing whether or not the mechanisms of the immunological damage to and destruction of the pancreatic β-cells is the same in all patients with autoimmune diabetes has important implications from a therapeutic viewpoint. Immunomodulatory therapies (such as anti-CD3), have been found to be efficacious in modulating the type 1 diabetes disease process (96). Because LADA is more common than classic childhood type 1 diabetes, it will be interesting to determine whether these treatments are similarly effective in LADA.

Previous studies in the NOD mouse, the BB rat, and in a human pilot trial had shown that parenteral insulin therapy protects against type 1 diabetes (97, 98). Two studies from Japan demonstrated better preservation of β-cell function with insulin compared with sulfonylurea in ICA-positive and anti-GAD-positive phenotypic type 2 diabetes subjects (99, 100). Additional studies are needed to determine whether the beneficial effects of insulin treatment in Japanese LADA patients (99, 100) can be extended to all patients with LADA.

Speculations have been presented regarding the value of thiazolidinediones in the treatment of LADA, not only because of their ability to improve insulin sensitivity, but also because of their antiinflammatory effect. Rosiglitazone has been reported to increase IL-4 and IL-10 levels and decrease nuclear factor-κB-binding activity in mononuclear cells, monocyte chemoattractant protein-1, soluble intercellular adhesion molecule-1, interferon-γ, IL-12, IL-18, TNF-α, and C-reactive proteins (101–106). If the decline in β-cell function in type 2 diabetes patients is in part a result of T cell-mediated autoimmune destruction of the β-cells, then the addition of an antiinflammatory medication, such as rosiglitazone, might slow the decline in β-cell function. In fact, rosiglitazone was recently reported to provide greater preservation of islet β-cell function in islet autoimmune LADA subjects (GADA+) compared with a group of LADA subjects treated with insulin alone during a 3-yr follow-up (107). We hypothesize that the preservation of β-cell function in this study and others may in part be attributed to the ability of rosiglitazone to suppress or decrease the autoimmune T cell-mediated destruction of the β-cells. Other antidiabetic agents that have emerged as putative protectors of β-cells include glucagon-like peptide-1 analogs and IL-1 receptor antagonist (108). Further testing is needed to determine the best initial and long-term treatment of autoimmune phenotypic type 2 diabetes.

Another potential treatment for diabetes is antigen-specific immunomodulation. A randomized, double-blind, placebo-controlled dose-finding phase IIa GAD vaccine study in LADA subjects demonstrated not only safety of the drug product, Diamyd, but also efficacy in preserving β-cell function in LADA (109). Subsequently, the same dose of GAD administered twice 28 d apart preserved C-peptide in classic childhood type 1 diabetes (110). A recently published 5-yr follow-up study of the 47 LADA patients who were given GAD-alum at escalating dosages showed that the treatment was safe and did not compromise β-cell function (111). The increase in fasting and stimulated C-peptide levels that had previously been reported after 6 months in the group given 20 μg was maintained during the 5 yr follow-up (111). Because of the possible differences in the immune system's recognition of β-cell antigens between LADA and type 1 diabetes, different islet antigens might be more important for modulating the autoimmune attack against the β-cells in type 1 diabetes compared with LADA. Thus, the success of antigen-based therapies may depend upon whether or not tolerance to the islet antigens is reinstated by the therapy.

We have hypothesized that antigen spreading is more restricted in autoimmune diabetes in adults than in childhood type 1 diabetes (16, 54) and that some antigens may be more important in the type 1 diabetes *vs.* LADA disease process and possibly vice versa. Treatment with some antigens might be efficacious in both autoimmune diabetes in adults and childhood type 1 diabetes, such as the GAD treatment mentioned above, whereas other antigens might be selectively effective in childhood type 1 diabetes or LADA. Because the prevalence of type 2 diabetes is high and is increasing rapidly, even if only 10% are LADA subjects, this is a population of patients two or three times larger than the classical childhood type 1 diabetes patient population, and thus the efficacy of specific treatment options, including insulin, thiazolidinediones, and immunomodulatory regimens, is very important.

Acknowledgments

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Disclosure Summary: All the authors have disclosed no conflict of interest pertinent to this publication.

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