

Latent Autoimmune Diabetes in Adults

Ramachandra G. Naik, Barbara M. Brooks-Worrell, and Jerry P. Palmer

Charles River Clinical Services Northwest (R.G.N.), Tacoma, Washington 98418; and Department of Medicine (B.M.B.-W., J.P.P.), Division of Endocrinology, Metabolism, and Nutrition, Department of Veterans Affairs Puget Sound Health Care System, University of Washington, Seattle, Washington 98108

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 evi-

dence 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 intracytoplasmic 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

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

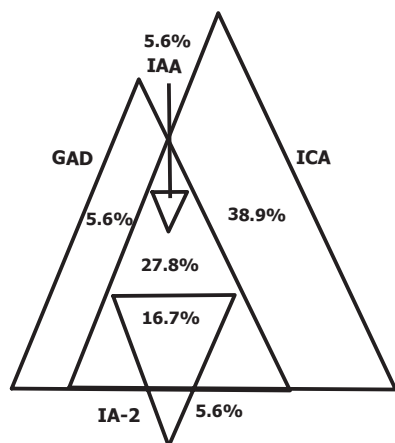


FIG. 1. Clustering of autoantibodies in autoantibody-positive patients. Numbers (%) refer to the percentage of the antibody-positive patients who were positive for the respective antibodies. [Reproduced with permission from R. Juneja *et al.*: *Metabolism* 50: 1008–1013, 2001 (18).]

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 NH₂-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-

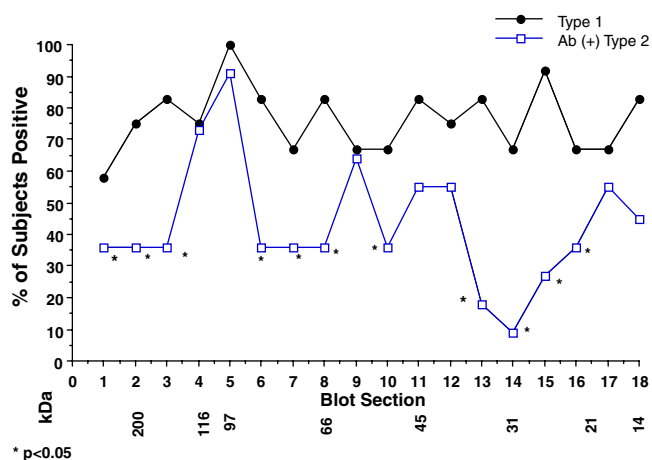


FIG. 2. T cell responses of 12 type 1 diabetes patients (closed circles) and 11 autoantibody-positive type 2 patients (type 1.5 patients; open squares). The percentage of subjects responding to each molecular mass region is shown. A positive response is taken as SI >2.0. Blot sections correspond to molecular 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-1 β , Fas, nuclear factor- κ B, 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-1 β 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 DQB1*0201 and 0302 confer increased risk of type 1 diabetes. It is also known that other HLA alleles including DR2 and DQB1*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 DQB1*0602 in subjects with LADA (79). The protection associated with DR2/DQB1*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-DQB1*0302 and the DR3/DR4-DQB1*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 presenta-

tion 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-DQB1 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- κ B-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 μ g 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

Address all correspondence and requests for reprints to: Jerry P. Palmer, M.D., Director of Endocrinology, Department of Veterans Affairs Puget Sound Health Care System, Professor of Medicine,

University of Washington, 1660 South Columbian Way (111), Seattle Washington 98108. E-mail: jpp@u.washington.edu.

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

References

1. Kuzuya T, Matsuda A 1997 Classification of diabetes on the basis of etiologies versus degree of insulin deficiency. *Diabetes Care* 20: 219–220
2. Service FJ, Rizza RA, Zimmerman BR, Dyck PJ, O'Brien PC, Melton 3rd LJ 1997 The classification of diabetes by clinical and C-peptide criteria: a prospective population-based study. *Diabetes Care* 20:198–201
3. Van der Auwera B, Van Waeyenberge C, Schuit F, Heimberg H, Vandewalle C, Gorus F, Flament J 1995 DRB1*0403 protects against IDDM in Caucasians with the high-risk heterozygous DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201 genotype. *Belgian Diabetes Registry. Diabetes* 44:527–530
4. Neifing JL, Greenbaum CJ, Kahn SE, McCulloch DK, Barmeier H, Lernmark A, Palmer JP 1993 Prospective evaluation of β -cell function in insulin autoantibody-positive relatives of insulin-dependent diabetic patients. *Metabolism* 42:482–486
5. McCulloch DK, Palmer JP 1991 The appropriate use of B-cell function testing in the preclinical period of type 1 diabetes. *Diabet Med* 8:800–804
6. Alberti KG, Zimmet PZ 1998 Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. *Diabet Med* 15:539–553
7. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997 Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197
8. Naik RG, Palmer JP 1997 Late-onset type 1 diabetes. *Curr Opin Endocrinol Diabetes* 4:308–315
9. Bottazzo GF, Florin-Christensen A, Doniach D 1974 Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet* 2:1279–1282
10. MacCuish AC, Irvine WJ, Barnes EW, Duncan LJP 1974 Antibodies to pancreatic islet cells in insulin-dependent diabetics with co-existent autoimmune disease. *Lancet* 2:1529–1531
11. Irvine WJ, Gray RS, McCallum CJ, Duncan LJP 1977 Clinical and pathogenic significance of pancreatic-islet-cell antibodies in diabetics treated with oral hypoglycaemic agents. *Lancet* 1: 1025–1027
12. Zimmet PZ 1995 The pathogenesis and prevention of diabetes in adults: genes, autoimmunity, and demography. *Diabetes Care* 18: 1050–1064
13. Kobayashi T 1994 Subtype of insulin-dependent diabetes mellitus (IDDM) in Japan: slowly progressive IDDM—the clinical characteristics and pathogenesis of the syndrome. *Diabetes Res Clin Pract* 24 Suppl:S95–S99
14. Kobayashi T, Tamemoto K, Nakanishi K, Kato N, Okubo M, Kajio H, Sugimoto T, Murase T, Kosaka K 1993 Immunogenetic and clinical characterization of slowly progressive IDDM. *Diabetes Care* 16:780–788
15. Groop LC, Bottazzo GF, Doniach D 1986 Islet cell antibodies identify latent type 1 diabetes in patients aged 35–75 years at diagnosis. *Diabetes* 35:1214–1219
16. Palmer JP, Hirsch IB 2003 What's in a name: latent autoimmune diabetes in adults, type 1.5, adult-onset, and type 1 diabetes. *Diabetes Care* 26:536–538
17. Cervin C, Lyssenko V, Bakhtadze E, Lindholm E, Nilsson P, Tuomi T, Cilio CM, Groop L 2008 Genetic similarities between latent autoimmune diabetes in adults, type 1 diabetes, and type 2 diabetes. *Diabetes* 57:1433–1437
18. Juneja R, Hirsch IB, Naik RG, Brooks-Worrell BM, Greenbaum CJ, Palmer JP 2001 Islet cell antibodies and glutamic acid decarboxylase antibodies but not the clinical phenotype help to identify type 1 1/2 diabetes in patients presenting with type 2 diabetes. *Metabolism* 50:1008–1013
19. Juneja R, Palmer JP 1999 Type 1 1/2 diabetes: myth or reality. *Autoimmunity* 29:65–83
20. Naik RG, Palmer JP 2003 Latent autoimmune diabetes in adults (LADA). *Rev Endocr Metab Disord* 4:233–241
21. Borg H, Gottsäter A, Landin-Olsson M, Fernlund P, Sundkvist G 2001 High levels of antigen-specific islet antibodies predict future β -cell failure in patients with onset of diabetes in adult age. *J Clin Endocrinol Metab* 86:3032–3038
22. Urakami T, Miyamoto Y, Matsunaga H, Owada M, Kitagawa T 1995 Serial changes in the prevalence of islet cell antibodies and islet cell antibody titer in children with IDDM of abrupt or slow onset. *Diabetes Care* 18:1095–1099
23. Nakanishi K, Kobayashi T, Miyashita H, Okubo M, Sugimoto T, Murase T, Kosaka K, Hara M 1993 Relationships among residual β cells, exocrine pancreas, and islet cell antibodies in insulin-dependent diabetes mellitus. *Metabolism* 42:196–203
24. Yeung V, Chan JCN, Chow CC, Zimmet P, Cockrum CS, Antibodies to glutamic acid decarboxylase (anti-GAD) in Chinese IDDM patients. *Proc 15th International Diabetes Federation Congress, Kobe, Japan, 1994*, p 432
25. Furlanos S, Dotta F, Greenbaum CJ, Palmer JP, Rolandsson O, Colman PG, Harrison LC 2005 Latent autoimmune diabetes in adults (LADA) should be less latent. *Diabetologia* 48:2206–2212
26. Palmer JP, Hampe CS, Chiu H, Goel A, Brooks-Worrell BM 2005 Is latent autoimmune diabetes in adults distinct from type 1 diabetes or just type 1 diabetes at an older age?. *Diabetes* 54:S62–S67
27. Rosenbloom AL 2003 Obesity, insulin resistance, β -cell autoimmunity, and the changing clinical epidemiology of childhood diabetes. *Diabetes Care* 26:2954–2956
28. Hathout EH, Thomas W, El-Shahawy M, Nahab F, Mace JW 2001 Diabetic autoimmune markers in children and adolescents with type 2 diabetes. *Pediatrics* 107:E102
29. Umpaichitra V, Banerji MA, Castells S 2002 Autoantibodies in children with type 2 diabetes mellitus. *J Pediatr Endocrinol Metab* 15:525–530
30. Kahn SE 2001 The importance of β -cell failure in the development and progression of type 2 diabetes. *J Clin Endocrinol Metab* 86: 4047–4058
31. Wenzlau JM, Moua O, Sarkar SA, Yu L, Rewers M, Eisenbarth GS, Davidson HW, Hutton JC 2008 SIC30A8 is a major target of humoral autoimmunity in type 1 diabetes and a predictive marker in prediabetes. *Ann NY Acad Sci* 1150:256–259
32. Tuomi T, Groop LC, Zimmet PZ, Rowley MJ, Knowles W, Mackay IR 1993 Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease. *Diabetes* 42:359–362
33. Hosszúfalusi N, Vatay A, Rajczy K, Prohászka Z, Pozsonyi E, Horváth L, Grosz A, Gerő L, Madácsy L, Romics L, Karádi I, Füst G, Pánczél P 2003 Similar genetic features and different islet cell autoantibody pattern of latent autoimmune diabetes in adults (LADA) compared with adult-onset type 1 diabetes with rapid progression. *Diabetes Care* 26:452–457
34. Murao S, Kondo S, Ohashi J, Fujii Y, Shimizu I, Fujiyama M, Ohno K, Takada Y, Nakai K, Yamane Y, Osawa H, Makino H 2008 Anti-thyroid peroxidase antibody, IA-2 antibody, and fasting C-peptide levels predict β cell failure in patients with latent autoimmune diabetes in adults (LADA). A 5 year follow-up of the Ehime study. *Diabetes Res Clin Pract* 80:114–121
35. Krischer JP, Cuthbertson DD, Yu L, Orban T, Maclaren N, Jackson R, Winter WE, Schatz DA, Palmer JP, Eisenbarth GS 2003 The Diabetes Prevention Trial-Type 1 Study Group: screening strategies for

- the identification of multiple antibody-positive relatives of individuals with type 1 diabetes. *J Clin Endocrinol Metab* 88:103–108
36. Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Chase HP, Eisenbarth GS 1996 Number of autoantibodies (against insulin, GAD or ICA512/IA2) rather than particular autoantibody specificities determines risk of type I diabetes. *J Autoimmun* 9:379–383
 37. Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Jackson RA, Chase HP, Eisenbarth GS 1996 Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. *Diabetes* 45:926–933
 38. Mayer A, Fabien N, Gutowski MC, Dubois V, Gebuhrer L, Biennu J, Orgiazzi J, Madec AM 2007 Contrasting cellular and humoral autoimmunity associated with latent autoimmune diabetes in adults. *Eur J Endocrinol* 157:53–61
 39. Zavala AV, Fabiano de Bruno LE, Cardoso AI, Mota AH, Capucchio M, Poskus E, Fainboim L, Basabe JC 1992 Cellular and humoral autoimmunity markers in type 2 (non-insulin-dependent) diabetic patients with secondary drug failure. *Diabetologia* 35:1159–1164
 40. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, Shattock M, Bottazzo GF, Holman R 1997 UKPDS 25. Autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. *Lancet* 350:1288–1293
 41. Rowley MJ, Mackay IR, Chen QY, Knowles WJ, Zimmet PZ 1992 Antibodies to glutamic acid decarboxylase discriminate major types of diabetes mellitus. *Diabetes* 41:548–551
 42. Lohmann T, Kellner K, Verlohren HJ, Krug J, Steindorf J, Scherbaum WA, Seissler J 2001 Titre and combination of ICA and autoantibodies to glutamic acid decarboxylase discriminate two clinically distinct types of latent autoimmune diabetes in adults (LADA). *Diabetologia* 44:1005–1010
 43. Borg H, Gottsäter A, Fernlund P, Sundkvist G 2002 A 12-year prospective study of the relationship between islet antibodies and β -cell function at and after the diagnosis in patients with adult-onset diabetes. *Diabetes* 51:1754–1762
 44. van Deutekom AW, Heine RJ, Simsek S 2008 The islet autoantibody titers their clinical relevance in latent autoimmune diabetes in adults (LADA) and the classification of diabetes mellitus. *Diabet Med* 25:117–125
 45. Buzzetti R, Di Pietro S, Giaccari A, Petrone A, Locatelli M, Suraci C, Capizzi M, Arpi ML, Bazzigalupi E, Dotta F, Bosi E 2007 High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. *Diabetes Care* 30:932–938
 46. Seissler J, de Sonnaville JJ, Morgenthaler NG, Steinbrenner H, Glawe D, Khoo-Morgenthaler UY, Lan MS, Notkins AL, Heine RJ, Scherbaum WA 1998 Immunological heterogeneity in type 1 diabetes: presence of distinct autoantibody patterns in patients with acute onset and slowly progressive disease. *Diabetologia* 41:891–897
 47. Hillman M, Törn C, Thorgeirsson H, Landin-Olsson M 2004 IgG4-subclass of glutamic acid decarboxylase antibody is more frequent in latent autoimmune diabetes in adults than in type 1 diabetes. *Diabetologia* 47:1984–1989
 48. Hampe CS, Kockum I, Landin-Olsson M, Törn C, Ortqvist E, Persson B, Rolandsson O, Palmer J, Lernmark A 2002 GAD65 antibody epitope patterns of patients with type 1.5 differ from that of type 1 diabetes patients. *Diabetes Care* 25:1481–1482
 49. Padoa CJ, Banga JP, Madec AM, Ziegler M, Schlosser M, Ortqvist E, Kockum I, Palmer J, Rolandsson O, Binder KA, Foote J, Luo D, Hampe CS 2003 Recombinant Fab of human monoclonal antibodies specific to the middle epitope of GAD65 inhibit type 1 diabetes-specific GAD65Abs. *Diabetes* 52:2689–2695
 50. Desai M, Cull CA, Horton VA, Christie MR, Bonifacio E, Lampasona V, Bingley PJ, Levy JC, Mackay IR, Zimmet P, Holman RR, Clark A 2007 GAD autoantibodies and epitope reactivities persist after diagnosis in latent autoimmune diabetes in adults but do not predict disease progression: UKPDS 77. *Diabetologia* 50:2052–2060
 51. Tiberti C, Giordano C, Locatelli M, Bosi E, Bottazzo GF, Buzzetti R, Cucinotta D, Galluzzo A, Falorni A, Dotta F 2008 Identification of tyrosine phosphatase 2 (256-760) construct as a new, sensitive marker for the detection of islet autoimmunity in type 2 diabetic patients. The Non-Insulin Requiring Autoimmune Diabetes (NIRAD) Study. *Diabetes* 57:1276–1283
 52. Brooks-Worrell B, Dosch HM, Herold K, Seyfert V, Greenbaum CJ, Gitelman SE, Palmer JP 2004 Marked differences in T cell reactivity in recently diagnosed type 1 diabetes patients versus controls. Proc 12th International Congress of Immunology and 4th Annual Conference of the Federation of Clinical Immunology Societies, Montreal, Canada
 53. Brooks-Worrell B, Warsen A, Palmer JP 2009 Improved T cell assay for identification of type 1 diabetes patients. *J Immunol Methods* 344:79–83
 54. Brooks-Worrell BM, Juneja R, Minokadeh A, Greenbaum CJ, Palmer JP 1999 Cellular immune responses to human islet proteins in antibody-positive type 2 diabetic patients. *Diabetes* 48:983–988
 55. Ismail H, Wotring M, Kimmie C, Au L, Palmer JP, Brooks-Worrell BM 2007 T cell-positive antibody-negative phenotypic type 2 patients, a unique subgroup of autoimmune diabetes. *Diabetes* 56(S1):A325
 56. Brooks-Worrell BM, Starkebaum GA, Greenbaum C, Palmer JP 1996 Peripheral blood mononuclear cells of insulin-dependent diabetic patients respond to multiple islet cell proteins. *J Immunol* 157:5668–5674
 57. Brooks-Worrell B, Gersuk VH, Greenbaum C, Palmer JP 2001 Inter-molecular antigen spreading occurs during the pre-clinical period of human type 1 diabetes. *J Immunol* 166:5265–5270
 58. Roep BO, Arden SD, de Vries RR, Hutton JC 1990 T cell clones from a type 1 diabetic patient respond to insulin secretory granule proteins. *Nature* 345:632–634
 59. Roep BO, Kallan AA, Duinkerken G, Arden SD, Hutton JC, Bruining GJ, de Vries RR 1995 T cell reactivity to β -cell membrane antigens associated with β cell destruction in IDDM. *Diabetes* 44:278–283
 60. Roep BO 1996 T cell responses to autoantigens in IDDM: The search for the Holy Grail. *Diabetes* 45:1147–1156
 61. Durinovic-Bellò I, Hummel M, Ziegler AG 1996 Cellular immune response to diverse islet cell antigens in IDDM. *Diabetes* 45:795–800
 62. Goel A, Chiu H, Felton J, Palmer JP, Brooks-Worrell B 2007 T cell responses to islet antigens improves detection of autoimmune diabetes and identifies patients with more severe β -cell lesions in phenotypic type 2 diabetes. *Diabetes* 56:2110–2115
 63. Tree TI, Roep BO, Peakman M 2006 A mini meta-analysis of studies on CD4+CD25+ T cells in human type 1 diabetes: report of the Immunology of Diabetes Society T Cell Workshop. *Ann NY Acad Sci* 1079:9–18
 64. Yang Z, Zhou Z, Huang G, Ling H, Yan X, Peng J, Li X 2007 The CD4+ regulatory T-cells is decreased in adults with latent autoimmune diabetes. *Diabetes Res Clin Pract* 76:126–131
 65. The Diabetes Control and Complications Trial Research Group 1998 Effect of intensive therapy on residual β -cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. *Ann Intern Med* 128:517–523
 66. Törn C, Landin-Olsson M, Lernmark A, Palmer JP, Arnqvist HJ, Blohmé G, Lithner F, Littorin B, Nyström L, Scherstén B, Sundkvist G, Wibell L, Ostman J 2000 Prognostic factors for the course of β cell function in autoimmune diabetes. *J Clin Endocrinol Metab* 85:4619–4623
 67. Gottsäter A, Landin-Olsson M, Fernlund P, Lernmark A, Sundkvist G 1993 β -Cell function in relation to islet cell antibodies during the first 3 yr after clinical diagnosis of diabetes in type II diabetic patients. *Diabetes Care* 16:902–910
 68. Behme MT, Dupre J, Harris SB, Hramiak IM, Mahon JL 2003 Insulin resistance in latent autoimmune diabetes of adulthood. *Ann NY Acad Sci* 1005:374–377
 69. Zinman B, Kahn SE, Haffner SM, O'Neill MC, Heise MA, Freed

- MI 2004 Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe. *Diabetes* 53:3193–3200
70. Chiu HK, Tsai EC, Juneja R, Stoever J, Brooks-Worrell B, Goel A, Palmer JP 2007 Equivalent insulin resistance in latent autoimmune diabetes in adults (LADA) and type 2 diabetes patients. *Diabetes Res Clin Pract* 77:237–244
 71. Davis TM, Zimmet P, Davis WA, Bruce DG, Fida S, Mackay IR 2000 Autoantibodies to glutamic acid decarboxylase in diabetic patients from a multi-ethnic Australian community: the Fremantle Diabetes Study. *Diabet Med* 17:667–674
 72. Hawa MI, Thivolet C, Mauricio D, Alemanno I, Cipponeri E, Collier D, Hunter S, Buzzetti R, de Leiva A, Pozzilli P, Leslie RD 2009 Metabolic syndrome and autoimmune diabetes: action LADA 3. *Diabetes Care* 32:160–164
 73. Donath MY, Ehses JA 2006 Type 1, type 1.5, and type 2 diabetes: NOD the diabetes we thought it was. *Proc Natl Acad Sci USA* 103:12217–12218
 74. Donath MY, Schumann DM, Faulenbach M, Ellingsgaard H, Perren A, Ehses JA 2008 Islet inflammation in type 2 diabetes. *Diabetes Care* 31(Suppl 2):S161–S164
 75. Pietropaolo M, Barinas-Mitchell E, Kuller LH 2007 The heterogeneity of diabetes. Unraveling a dispute: is systemic inflammation related to islet autoimmunity? *Diabetes* 56:1189–1197
 76. Gleichmann H, Zörcher B, Greulich B, Gries FA, Henrichs HR, Betrams J, Kolb H 1984 Correlation of islet cell antibodies and HLA-DR phenotypes with diabetes mellitus in adults. *Diabetologia* 27:90–92
 77. Chiu HK, Palmer JP 2004 Autoimmune diabetes: more than just one flavor? *J Endocrinol Invest* 27:480–484
 78. Sanjeevi CB, Gambelunghé G, Falorni A, Shtauvere-Brameus A, Kanungo A 2002 Genetics of latent autoimmune diabetes in adults. *Ann NY Acad Sci* 958:107–111
 79. Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A, Nissén M, Ehrnström BO, Forsén B, Snickars B, Lahti K, Forsblom C, Saloranta C, Taskinen MR, Groop LC 1999 Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. *Diabetes* 48:150–157
 80. Cosentino A, Gambelunghé G, Tortoioli C, Falorni A 2002 CTLA-4 gene polymorphism contributes to the genetic risk for latent autoimmune diabetes in adults. *Ann NY Acad Sci* 958:337–340
 81. Cerrone GE, Caputo M, Lopez AP, González C, Massa C, Cédola N, Targovnik HM, Frechtel GD 2004 Variable number of tandem repeats of the insulin gene determines susceptibility to latent autoimmune diabetes in adults. *Mol Diagn* 8:43–49
 82. Törn C, Gupta M, Nikitina Zake L, Sanjeevi CB, Landin-Olsson M 2003 Heterozygosity for MICA5.0/MICA5.1 and HLA-DR3-DQ2/DR4-DQ8 are independent genetic risk factors for latent autoimmune diabetes in adults. *Hum Immunol* 64:902–909
 83. Vatay A, Rajczyk K, Pozsonyi E, Hosszúfalusi N, Prohászka Z, Füst G, Karádi I, Szalai C, Grósz A, Bártfai Z, Pánczél P 2002 Differences in the genetic background of latent autoimmune diabetes in adults (LADA) and type 1 diabetes mellitus. *Immunol Lett* 84:109–115
 84. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P 2007 A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 445:881–885
 85. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina-Olsson L, Ding CJ, Swift AJ, Narisu N, Hu T, Pruim R, Xiao R, Li XY, Conneely KN, Riebow NL, Sprau AG, Tong M, White PP, Hetrick KN, Barnhart MW, Bark CW, Goldstein JL, Watkins L, Xiang F, Saramies J, Buchanan TA, Watanabe RM, Valle TT, Kinnunen L, Abecasis GR, Pugh EW, Doheny KF, Bergman RN, Tuomilehto J, Collins FS, Boehnke M 2007 A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 316:1341–1345
 86. Saxena R, Voight BF, Lyssenko V, Burt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjögren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S 2007 Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 316:1331–1336
 87. Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, Timpson NJ, Perry JR, Rayner NW, Freathy RM, Barrett JC, Shields B, Morris AP, Ellard S, Groves CJ, Harries LW, Marchini JL, Owen KR, Knight B, Cardon LR, Walker M, Hitman GA, Morris AD, Doney AS, McCarthy MI, Hattersley AT 2007 Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* 316:1336–1341
 88. Staiger H, Machicao F, Stefan N, Tschrötter O, Thamer C, Kantartzis K, Schäfer SA, Kirchhoff K, Fritsche A, Häring HU 2007 Polymorphisms within novel risk loci for type 2 diabetes determine β -cell function. *PLoS ONE* 2:e832
 89. Kirchhoff K, Machicao F, Haupt A, Schäfer SA, Tschrötter O, Staiger H, Stefan N, Häring HU, Fritsche A 2008 Polymorphisms in the TCF7L2, CDKAL1, and SLC30A8 genes are associated with impaired proinsulin conversion. *Diabetologia* 51:597–601
 90. Boesgaard TW, Zilinskaite J, Väntinen M, Laakso M, Jansson PA, Hammarstedt A, Smith U, Stefan N, Fritsche A, Häring H, Hribal M, Sesti G, Zobel DP, Pedersen O, Hansen T 2008 The common SLC30A8 Arg325Trp variant is associated with reduced first-phase insulin release in 846 non-diabetic offspring of type 2 diabetes patients: the EUGENE2 study. *Diabetologia* 51:816–820
 91. Wenzlau JM, Liu Y, Yu L, Moua O, Fowler KT, Rangasamy S, Walters J, Eisenbarth GS, Davidson HW, Hutton JC 2008 A common nonsynonymous single nucleotide polymorphism in the SLC30A8 gene determines ZnT8 autoantibody specificity in type 1 diabetes. *Diabetes* 57:2693–2697
 92. Grill V, Persson G, Carlsson S, Norman A, Alvarsson M, Ostensson CG, Svanström L, Efendic S 1999 Family history of diabetes in middle-age Swedish men is a gender unrelated factor which associates with insulinopenia in newly diagnosed diabetes subjects. *Diabetologia* 42:15–23
 93. Meigs JB, Cupples LA, Wilson PW 2000 Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes* 49:2201–2207
 94. Bonifacio E, Hummel M, Walter M, Schmid S, Ziegler AG 2004 IDDM1 and multiple family history of type 1 diabetes combine to identify neonates at high risk for type 1 diabetes. *Diabetes Care* 27:2695–2700
 95. Carlsson S, Midthjell K, Grill V 2007 Influence of family history of diabetes on incidence and prevalence of latent autoimmune diabetes of the adult: results from the Nord-Trøndelag Health Study. *Diabetes Care* 30:3040–3045
 96. Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, Gitelman SE, Harlan DM, Xu D, Zivin RA, Bluestone JA 2002 Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N Engl J Med* 346:1692–1698
 97. Bertrand S, De Paeppe M, Vigeant C, Yale JF 1992 Prevention of adoptive transfer in BB rats by prophylactic insulin treatment. *Diabetes* 41:1273–1277
 98. Gotfredsen CF, Buschard K, Frandsen EK 1985 Reduction of di-

- abetes incidence of BB Wistar rats by early prophylactic insulin treatment of diabetes-prone animals. *Diabetologia* 28:933–935
99. Kobayashi T 2001 Multicenter prevention trial of slowly progressive IDDM with small dose of insulin (the Tokyo Study). *Diabetes Metab Res Rev* 17 (Suppl):S29
 100. Kobayashi T, Maruyama T, Shimada A, Kasuga A, Kanatsuka A, Takei I, Tanaka S, Yokoyama J 2002 Insulin intervention to preserve β cells in slowly progressive insulin-dependent (type 1) diabetes mellitus. *Ann NY Acad Sci* 958:117–130
 101. Cuzzocrea S, Pisano B, Dugo L, Ianaro A, Maffia P, Patel NS, Di Paola R, Ialenti A, Genovese T, Chatterjee PK, Di Rosa M, Caputi AP, Thiemermann C 2004 Rosiglitazone, a ligand of the peroxisome proliferator-activated receptor- γ , reduces acute inflammation. *Eur J Pharmacol* 483:79–93
 102. Ramakers JD, Verstege MI, Thuijls G, Te Velde AA, Mensink RP, Plat J 2007 The PPAR γ agonist rosiglitazone impairs colonic inflammation in mice with experimental colitis. *J Clin Immunol* 27: 275–283
 103. Mohanty P, Aljada A, Ghanim H, Hofmeyer D, Tripathy D, Syed T, Al-Haddad W, Dhindsa S, Dandona P 2004 Evidence for a potent anti-inflammatory effect of rosiglitazone. *J Clin Endocrinol Metab* 89:2728–2735
 104. Kim HJ, Kang ES, Kim DJ, Kim SH, Ahn CW, Cha BS, Nam M, Chung CH, Lee KW, Nam CM, Lee HC 2007 Effects of rosiglitazone and metformin on inflammatory markers and adipokines: decrease in interleukin-18 is an independent factor for the improvement of homeostasis model assessment- β in type 2 diabetes mellitus. *Clin Endocrinol (Oxf)* 66:282–289
 105. Abdin AA, Baalash AA, Homooda HE 26 March 2009 Effects of rosiglitazone and aspirin on experimental model of induced type 2 diabetes in rats: focus on insulin resistance and inflammatory markers. *J Diabetes Complications* 10.016/j.jdiacomp.2009.01.005
 106. Esposito K, Ciotola M, Carleo D, Schisano B, Saccomanno F, Sasso FC, Cozzolino D, Assaloni R, Merante D, Ceriello A, Giugliano D 2006 Effect of rosiglitazone on endothelial function and inflammatory markers in patients with the metabolic syndrome. *Diabetes Care* 29:1071–1076
 107. Yang Z, Zhou Z, Li X, Huang G, Lin J 2009 Rosiglitazone preserves islet β -cell function of adult-onset latent autoimmune diabetes in 3 years follow-up study. *Diabetes Res Clin Pract* 83:54–60
 108. Larsen CM, Faulenbach M, Vaag A, Vølund A, Ehres JA, Scifert B, Mandrup-Poulsen T, Donath MY 2007 Interleukin-1 receptor antagonist in type 2 diabetes. *N Engl J Med* 356:1517–1526
 109. Agardh CD, Cilio CM, Lethagen A, Lynch K, Leslie RD, Palmér M, Harris RA, Robertson JA, Lernmark A 2005 Clinical evidence for the safety of GAD65 immunomodulation in adult-onset autoimmune diabetes. *J Diabetes Complications* 19:238–246
 110. Ludvigsson J, Faresjö M, Hjorth M, Axelsson S, Chéramy M, Pihl M, Vaarala O, Forsander G, Ivarsson S, Johansson C, Lindh A, Nilsson NO, Aman J, Orqvist E, Zerhouni P, Casas R 2008 GAD treatment and insulin secretion in recent-onset type 1 diabetes. *N Engl J Med* 359:1909–1920
 111. Agardh CD, Lynch KF, Palmér M, Link K, Lernmark A 2009 GAD65 vaccination: 5 years of follow-up in a randomised dose-escalating study in adult-onset autoimmune diabetes. *Diabetologia* 10.1007/s00125-009-1371-2