Autoimmune Diabetes Not Requiring Insulin at Diagnosis (Latent Autoimmune Diabetes of the Adult)

Definition, characterization, and potential prevention

PAOLO POZZILLI, MD[1]
UMBERTO DI MARIO, MD[2]

Type 1 diabetes is caused by the immune-mediated destruction of islet insulin-secreting β-cells. This chronic destructive process is associated with both cellular and humoral immune changes in the peripheral blood that can be detected months or even years before the onset of clinical diabetes. Throughout this prediabetic period, metabolic changes, including altered glucose tolerance and reduced insulin secretion, deteriorate at variable rates and eventually result in clinical diabetes. A fraction of individuals with humoral immunological changes have clinical diabetes that initially is not insulin-requiring. The onset of diabetes in these patients is usually in adult life, and because their diabetes is at least initially not insulin-requiring, they appear clinically to be affected by type 2 diabetes. Such patients probably have the same disease process as patients with type 1 diabetes in that they have similar HLA genetic susceptibility as well as autoantibodies to islet antigens, low insulin secretion, and a higher rate of progression to insulin dependency. These patients are defined as being affected by an autoimmune type of diabetes not requiring insulin at diagnosis, which is also named latent autoimmune diabetes of the adult (LADA). Special attention should be paid to diagnose such patients because therapy may influence the speed of progression toward insulin dependency, and in this respect, efforts should be made to protect residual C-peptide secretion. LADA can serve as a model for designing new strategies for prevention of type 1 diabetes but also as a target group for prevention in its own right.

Diabetes Care 24:1460–1467, 2001

DEFINITION AND PATHOGENESIS — The recent new classification of diabetes is the third attempt in the last 30 years to recomprise the many different disease entities comprised in the term diabetes under a single classification criterion (1). Age was the main classification criterion in the early 1970s, and it was soon abandoned because the different forms of diabetes can be present at any age, although a few are typical of young age and others of adult age. Insulin dependency, a clinical criterion, was then used because of its ease of use in a clinical setting, and it was considered for subgrouping cases with different pathogenetic mechanisms.

For many years (maybe too many), insulin dependency was thought to specifically characterize those forms of diabetes with an autoimmune pathogenesis. More recently, attention has been paid to the fact that the clinical criterion (i.e., insulin dependency, and the pathogenetic criterion, i.e., the presence of autoimmune mechanisms leading to β-cell damage) do not match in a number of cases. An etiologic classification criterion was therefore chosen to subgroup the different types of diabetes (1). Type 1 diabetes is characterized by the destruction of the insulin-secreting β-cells of the islets of Langerhans, by the production of little or no insulin, and, in most cases, by immune-mediated pathogenetic mechanisms highlighted by the presence of islet cell autoantibodies and by an altered frequency of immune-regulating genes in the HLA region. This form of diabetes often develops in children, although it may occur at any age and often, but not always, requires insulin treatment. Type 2 diabetes develops in adult age and is characterized by insufficient insulin secretion with or without insulin resistance. This form of diabetes does not present autoimmune phenomena and usually, but not always, does not require insulin. For a clinician, the distinction between type 1 and type 2 diabetes is not always straightforward. The presence or absence of islet autoantibodies is one of the more direct ways to distinguish between type 1 and type 2 diabetic patients. If a search is done for these autoantibodies in all new cases of diabetes, it is now believed that among the non–insulin-requiring diabetic subjects at diagnosis, a significant minority are islet cell antibody–positive (2). These patients who clinically are difficult to distinguish from type 2 diabetic subjects test positive for those markers that characterize patients with type 1 diabetes.

The term latent autoimmune diabetes in adults (LADA) was introduced to define adult diabetic patients initially non–insulin-requiring but with immune markers of type 1 diabetes that, in a number of cases, progress to insulin dependency (3). This term has been largely used in the last few years when referring to autoimmune forms of diabetes not requiring insulin initially. Now it is clear that diabetes in these patients is not latent and is not limited to adults. Some have called this form of disease slow-progressing type 1 diabetes (4), but a slow progression of β-cell destruction can be considered as only one of the possible explanations.

From the [1]Università Campus Biomedico and the [2]Università La Sapienza, Rome, Italy.
Address correspondence and reprint requests to Prof. P. Pozzilli, Università Campus Biomedico, Via Longoni 83, 00155 Rome, Italy. E-mail: p.pozzilli@caspur.it.
Received for publication 18 January 2001 and accepted in revised form 26 April 2001.
Abbreviations: ICA, islet cell antibodies; LADA, latent autoimmune diabetes of the adult; SU, sulfonylurea; UKPDS, U.K. Prospective Diabetes Study.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Pathogenesis of LADA*

Factors involved in partial and/or slow progression of β-cell destruction
Genetic predisposition to type 1 diabetes less marked
Possible contribution of protective genes toward β-cell destruction
Partial regeneration of β-cells
Induction of immune tolerance once the immune process toward β-cells has initiated
Quantitative/qualitative reduction in the exposure to environmental factors damaging the β-cells

Some have suggested that type 1 diabetes and LADA are distinct disease processes, although both are autoimmune in nature, and have coined the term 1.5 diabetes (5). In our opinion, the term autoimmune diabetes not requiring insulin at diagnosis (or LADA) is more appropriate in that the concept of latency indicates patients of adult age who do not require insulin at least for some time after diagnosis and who possess immunological and genetic features typical of type 1 diabetes.

The question regarding the pathogenesis of LADA still remains unanswered (Table 1). Based on available data that is limited to the Caucasian population, evidence suggests that in LADA, the typical HLA genetic predisposition to type 1 diabetes is less marked than that in patients diagnosed in younger age (6). As such, this finding could be sufficient to explain the age of onset in adults. Hyperglycemia in type 1 diabetes is thought to be the end-stage result of an interaction between susceptibility genes and an abnormal immune response toward β-cells after exposure to some environmental factors not yet characterized (7). We can speculate that in the case of LADA, the qualitative/quantitative exposure to such factors is less pronounced. There are several common features between LADA and type 1 diabetes, including T-cell "insulitis," which has been found in a patient with GAD antibodies and residual β-cell function (8) who had a pancreas biopsy, suggesting that the pathological hallmark of type 1 diabetes (i.e., insulitis) is present in LADA. However, immune tolerance to β-cell antigens could occur in LADA, which in turn may spontaneously protect these patients from extensive T-cell destruction of β-cells. In addition, some patients with LADA may have clinical or subclinical autoimmune endocrinopathies (thyroid and adrenal). In such cases, antibodies to other endocrine tissues are also detectable, and therefore, these patients are better classified as affected by the autoimmune polyendocrine syndrome (9).

The progression toward β-cell destruction probably varies according to the age when hyperglycemia is diagnosed, as shown by the residual β-cell function found at diagnosis (4). In the very young, a linear and rapid progression toward exhaustion of the β-cell function is likely to occur, whereas in the adolescent, a longer prodrome followed by an acute precipitating factor (viral?) may be more common, based on available data (10). In LADA, we can speculate that multiple events may hit the β-cells in genetically susceptible subjects, leading to the decline of β-cell function. This could be one of the possible pathogenic mechanisms. Overall, the age at diagnosis influences the amount of β-cell mass left, which is clearly more elevated in patients with LADA as opposed to the adolescent or the very young, in whom residual C-peptide secretion is indeed very low (11) (Fig. 1).

CHARACTERIZATION OF LADA

— LADA patients have several features of classic type 1 diabetes in addition to islet cell antibody positivity, including high rates of HLA-DR3 and DR4 (12–15). Adults with non–insulin-requiring diabetes who are positive for GAD and/or islet cell antibodies (ICA) require insulin treatment significantly earlier after diagnosis than ICA$^-$ patients (16,17). Of the adult diabetic patients considered to be insulin-deficient on the basis of their C-peptide responses to glucagon, antibodies to GAD are detected in 75% compared with ~10% in the non–insulin-deficient group (17). The type of autoantibodies to islet cell antigens distinguish between acute-onset type 1 diabetes and LADA because GAD antibodies and ICA indicate slow disease progression, whereas the presence of IA-2 antibodies is associated with an acute-onset clinical phenotype (18). Patients with LADA share insulin resistance with type 2 diabetic patients but display a more severe defect in maximally stimulated β-cell capacity (19).

Immune markers

The prevalence of LADA has been estimated in a number of studies of both European and non-European populations (Table 2). A wide variation has been described, partly depending on the markers chosen to define the condition but also on the characteristics of the patients (e.g., newly diagnosed or previously diagnosed). In the early 1980s, immune abnormalities (presence of ICA) in diabetic patients not requiring insulin at diagnosis were reported (20), but a better idea of frequency of LADA is available from a European population-based study of

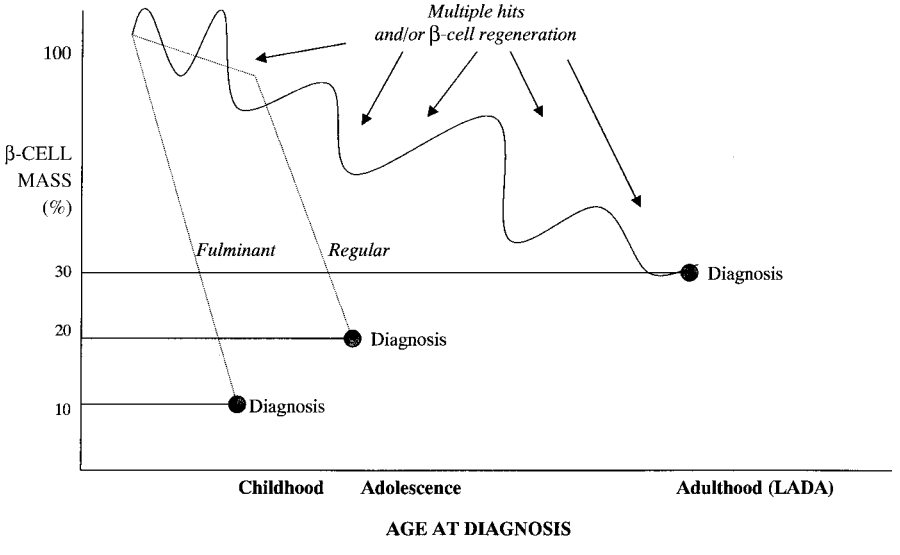

Figure 1—*The destruction of β-cells and the appearance of type 1 diabetes according to the age of onset and the putative pathogenetic mechanisms.*

Table 2—*Recent European population-based studies of GAD antibody positivity in patients with LADA*

Reference number	Country	Study type	Ages (years)	Duration (*n*)	Other inclusions	Prevalence
34	Italy	Population-based	30–54	All new diabetes (130)	BMI <25	22.3% overall
24	Italy	Population-based	>40	(2,076)	Impaired/normal OGTT	2.8%, 0.6 impaired OGTT, 1% normal OGTT
23	Finland	Population-based	28–83	All duration NIR (1,122)	FBG ≥6.1 or 2-h ≥10.0 on OGTT	9.3% overall, 19.3% ≥45 years of age, 8.2% >45 years of age
32	Sweden	Consecutive clinic referrals	40–75	All new diabetes (203)		8% overall, 3.2% in NIR
35	U.K.	Representative population	25–65	New NIR (3,672)	Caucasian	10% overall, 34% 25–34 years of age, 7% 55–65 years of age
33	Holland	Population sample	50–74	General population, all known diabetes, screened diabetes (2,350)	GAD antibody positivity if >99th percentile of entire population	3.5% (0.7–10.0% CI) in known diabetes, 0% (0-3.3% CI) in screened diabetes
15	Finland	General practitioner referrals from defined population	45–64	New NIR (133)	Confirmed by OGTT	9%

NIR, non–insulin-requiring diabetes; OGTT, oral glucose tolerance test.

recently diagnosed adult diabetic patients (21) in whom 82% developed insulin dependency within 4 years of the initial diagnosis. Worldwide studies have identified some 10–20% of non–insulin-requiring diabetic patients with ICA and GAD antibodies (15,17,22).

At diagnosis, both ICA and GAD antibodies were shown to be predictors of insulin dependency, but GAD antibodies appeared to have higher sensitivity as predictors than ICA (23). In the population-based Cremona study in Italy, a sample of 2,076 people aged ≥40 years were classified as having diabetes, impaired glucose tolerance, or normal glucose tolerance. Antibodies to GAD were found in 2.8% of those with diabetes, whereas autoantibodies to IA2 were detected in only four subjects, two of whom had GAD antibodies (24). This low antibody prevalence may reflect the lower genetic predisposition of the continental Italian population to type 1 diabetes in general (25). The comparison of studies measuring GAD antibodies in non-European populations has shown that these antibodies are rare in Filipinos or patients of African origin (26,27). Similarly, a study examining the prevalence of type 2 diabetes in Papua New Guinea found an absence of GAD antibodies, indicating the low autoimmune component in this ethnic group (28). In contrast, up to 16% of Chinese type 2 diabetic patients were found to be GAD antibody–positive (29), and the frequency of positivity was reportedly not associated with the duration of the disease. In a Japanese study of 289 patients classified at clinical onset as having non–insulin-requiring diabetes, those treated with insulin were younger than those still not requiring insulin treatment, and 47% had GAD antibodies. Of the non–insulin-treated patients, 10% with a duration of disease <5 years had GAD antibodies, in contrast to only 3% with a longer duration of diabetes (30).

Prevalence studies involving populations not only within Europe but within the same European region also demonstrate a wide variation of LADA estimates. In their Swedish study, Gottsäter et al. (31) found that at onset, 24% of non–insulin-treated patients had GAD antibodies. Another Swedish study (32) reported that the prevalence of GAD antibodies was 8% overall in newly diagnosed diabetic patients and only 3.2% in patients classified as having type 2 diabetes. A Dutch population-based study (33) found GAD antibody positivity in 3.5% (95% CI 0.7–10%) of patients already known to have diabetes (type 1 or type 2), whereas, although different criteria were used, a higher prevalence of GAD positivity (>20%) was observed in Northern Italy (34). In the U.K. Prospective Diabetes Study (UKPDS), the largest study to date, antibodies to GAD and ICA were measured in patients with non–insulin-requiring diabetes for prediction of subsequent insulin requirement (35). Among these patients, the HLA genotype of those with ICA or GAD antibodies was similar to that of type 1 diabetic patients, and both the clinical phenotype and antibodies predicted insulin requirement. Reasons for variations in GAD positivity and predictive value toward insulin requirement are study design and inclusion criteria, i.e., differences in age, distance from diagnosis, and selection of patients (from clinic or general population). Table 2 summarizes the characteristics of recent European population-based studies describing GAD antibody prevalence in non–insulin-requiring diabetes. A number of other factors contribute to the observed differences in estimated European prevalence of GAD antibodies. These factors include the sensitivity and specificity of antibody assay methods, selection of

threshold criteria for GAD antibody positivity, selection of BMI or C-peptide level criteria, and the inclusion of patients of non-European origin. The lack of a standardized approach to the estimation of GAD antibody prevalence prevents the direct comparison of existing data between studies or countries. Such a comparison could be extremely useful for establishing the size of the LADA population and to see whether the prevalence of LADA differs in different countries, as in the case of type 1 diabetes diagnosed in individuals <15 years of age (25).

It is apparent from existing data that LADA could represent a sizeable proportion of diabetic patients. Accurate estimates of prevalence have important connotations not only for the correct classification of diabetes but also for the potential of developing early intervention strategies and estimating the scale of the public health problem that this subtype of diabetes represents.

Genetic markers

The presence of HLA-DQB1*0302 identifies patients at high risk of requiring insulin treatment (6). Diabetic patients who are at a relatively low risk of progression to insulin dependency would have a diabetes duration of >5 years, normal to high C-peptide levels, and the protective genetic haplotypes HLA-DQB1*0602 and HLA-DQA1*0102 (12,14,16). The situation is different in patients with evidence of islet cell autoimmunity at >65 years of age, as recently reported (36). Thus, among these patients, 12% showed GAD and IA2 antibodies, and the large majority was overweight and had normal insulinemia. This subgroup of autoimmune diabetic patients can remain free of insulin for a long period. Of the familial risk for type 1 diabetes, 42% has been linked to the IDDM1 locus in the HLA class II region on chromosome 6p21 (37), whereas 10% has been linked to the IDDM2 locus in the promoter region of the insulin gene on chromosome 11p 15.5. In addition, several other gene loci have been suggested to contribute to the genetic susceptibility to type 1 diabetes. Whether such susceptibility genes outside the HLA region play the same role in the etiology of LADA is unclear because no studies have been carried out in LADA patients. As far as HLA is concerned, the prevalence of HLA-DQB1*0201/0302 and HLA-DR3/DR4 seems to be age-related (13,37). Compared with younger patients, individuals older than 20 years at onset of type 1 diabetes are less often heterozygous for HLA-DQB1*0201/0302 (20%) and HLA-DR3/DR4 (12.5–24%) (38,39). However, in a recent study, no difference in genotype frequencies was observed between the young-onset and adult-onset type 1 diabetic patients (23).

Of note, the frequency of HLA-DQB1*0201/0302 was lower in GAD antibody–positive diabetic patients (12%) compared with both young-onset (34%) and adult-onset (41%) type 1 diabetic patients, although it did not differ from the frequency of DR3/DR4 in adult-onset patients in another Finnish study (12.5%) (39). Also, the proportion of GAD antibody–positive non–insulin-requiring diabetic patients possessing genotypes including HLA-DQB1*0302 or 0602 (12) was clearly different from the proportion of type 1 diabetic patients possessing the same genotypes, whereas no difference was observed in the genotype frequencies between the two type 1 diabetic groups. This observation confirms previous data that age at onset of diabetes is not affected by the presence of either the protective HLA-DR2 and HLA-DQB1*0602 (12) or the susceptibility-increasing HLA-DR4 and HLA-DQB1*0302 (38,39). However, in contrast to the studies mentioned above, another study from Germany (although small) reported that only 17% of 24 adults >40 years of age at onset of type 1 diabetes had HLA-DQB1*0302, whereas 21% had HLA-DQB1*0602 (40). It is unclear whether these frequencies could be affected by the low antibody positivity rate in the study patients. Therefore, the prevalence of the HLA-DQB1*0201/0302 (DR3/DR4) genotype may reflect the age at onset of diabetes, whereas the 0302 genotype is associated with type 1 diabetes, irrespective of the age at onset, at least in Sweden (23). Whether these age-dependent differences reflect different environmental influences remains unclear. Thus, in trials testing rates of disease progression to insulin dependency, age, duration of diabetes, C-peptide levels, BMI, ICA, and protective genetic haplotypes HLA-DQB1*0602 and HLA-DQA1*0102 should be assessed to calculate the required sample size.

SCREENING FOR LADA — Measurement of GAD antibodies in patients with recent-onset type 2 diabetes is, in practical terms, the first step in identifying patients who may be diagnosed with LADA if results are positive.

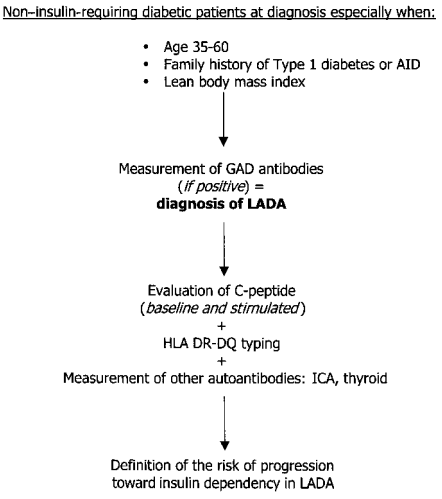

Figure 2—*Suggested steps for the characterization of LADA. AID, autoimmune diseases.*

Data from the UKPDS (35) has clearly shown that in diabetic patients aged between 35 and 45 years, most who test positive for both GAD and ICA progress rapidly toward insulin dependency. Whether progression is a consequence of the natural history of the disease in this age range or is due to inappropriate treatment in these patients is unknown (see MANAGEMENT OF LADA). Although the clinical utility of identifying GAD antibody–positive patients who undergo HLA typing and C-peptide measuring is not established, screening for GAD antibodies, in our opinion, should be considered. Thus, in the case of a positive result for GAD antibodies, the patient should be investigated in depth to characterize the disease status. HLA typing may help to support the diagnosis of LADA, baseline C-peptide evaluation can stage β-cell function, and C-peptide monitoring can help the physician to establish if and when to introduce insulin therapy (Fig. 2). However, before recommending this diagnostic strategy to physicians, further studies are required.

In patients with GAD autoantibodies, endocrine autoimmunity toward other cell types is often reported (41); therefore, measurement of autoantibodies to thyroid and adrenal cells can be a useful tool to spot latent autoimmune-associated endocrinopathies. As shown in Fig. 2, a number of clinical and family history con-

siderations should apply before measuring these antibodies. Thus, the presence of autoimmunity in relatives is a useful parameter, whereas lean BMI could be indicative of a rapid progression toward insulin dependency, although body weight per se is not typical of LADA as obese LADA patients have been described (19). In the case of GAD antibody positivity, a definition of the stage of the disease process is required and should include evaluation of C-peptide, HLA status, and other autoantibodies measurement to adopt the correct therapeutic strategy. Because some LADA patients may be insulin-resistant, C-peptide measurement in individual cases may not be helpful. HLA typing, although useful, may be very expensive.

MANAGEMENT OF LADA —

There is no established intervention for patients with LADA, despite the fact that they represent a sizeable number of patients with diabetes. Because these patients are hyperglycemic, there is no doubt that they require specific therapy to control blood glucose. The best therapeutic option in LADA patients (while waiting for trials to prevent β-cell exhaustion) is to achieve good metabolic control and prevent chronic complications. It should be mentioned that glycemic control is a stronger risk factor for cardiovascular disease in LADA patients than in patients with type 2 diabetes and could be related to the lower prevalence of the metabolic syndrome observed in the former (42). In patients initially diagnosed as type 2 diabetic, a number of therapeutic options are possible that coincide with present available treatments of hyperglycemia. It is not the aim of this review to suggest what is the best hypoglycemic treatment for LADA patients; however, we will briefly comment on the pros and cons of the currently available family of drugs for treating hyperglycemia. Except for a pilot trial with insulin (see below), there are no clinical data so far to indicate that there is one specific treatment that is superior for LADA patients; therefore, at present, LADA is treated like type 2 diabetes.

Sulfonylureas

Beside diet, sulfonylureas (SUs) are largely used in patients with type 2 diabetes (43). SUs stimulate insulin secretion by promoting closure of the ATP-dependent potassium channels on pancreatic β-cells. SUs are good first-choice agents in type 2 diabetic patients, and LADA patients may also be included. Whereas initially controlling blood glucose, such treatment of LADA might favor early exhaustion of β-cell function because of the stimulatory effect of insulin secretion mediated by SUs. Because of their insulin-enhancing effect, weight gain is often a consequence of treatment with SUs, resulting in a continuous stimulation of endogenous β-cells. In this respect, it should be underlined that in experimental models of autoimmune diabetes, stimulation of insulin secretion is associated with the release of insulin-associated secretory granules possessing antigenic property (44). It may be argued that activated immune response toward β-cell antigens, as in LADA patients, could be amplified using SUs as treatment for hyperglycemia in LADA patients. Although no contrary data are available, it can be speculated that SU therapy could in turn speed the progression toward β-cell destruction and the need to introduce insulin therapy to control hyperglycemia.

Metformin

Metformin is widely used to improve glycemic control in patients with type 2 diabetes. It does not stimulate insulin secretion or induce hypoglycemia and does not promote weight gain. Gluconeogenesis is suppressed, and stimulation of peripheral glucose uptake is increased (45). Such characteristics are useful in the typical obese type 2 diabetic patient (46) but also in nonobese individuals with type 2 diabetes. Furthermore, one potential problem associated with the use of metformin is the development of lactic acidosis in a patient at high risk of becoming insulin-dependent. Metformin has been tested in an experimental model of autoimmune diabetes; however, it did not affect the course of the disease as well as the lymphocytic infiltration in the islets of the NOD mouse (47), indicating that this compound does not interfere with the pathogenic process leading to β-cell destruction. Nevertheless, by controlling blood glucose levels, metformin may be able to protect β-cells from continuous hyperstimulation of insulin secretion if it is used in patients who do not sufficiently control blood glucose levels with diet alone.

POTENTIAL STRATEGIES FOR PREVENTING β-CELL DESTRUCTION IN LADA —

Assuming the disease process in LADA is similar to that of type 1 diabetes, though less destructive, prevention of β-cells from complete destruction should be attempted.

LADA can serve as a model for prevention of type 1 diabetes but also as a target group for prevention in its own right. Islet β-cell function is often partially preserved at the onset of type 1 diabetes, particularly in the older-onset patients (48). There is evidence that residual β-cell function can be preserved. Nicotinamide can per se maintain C-peptide secretion in recent-onset type 1 diabetic patients of adult age for at least 1 year after diagnosis (49). Protection of C-peptide secretion is important. For example, a study of patients with type 1 diabetes found that individuals who secreted C-peptide had lower HbA_{1c} levels and less microvascular complications (proteinuria and retinopathy) than those who did not secrete C-peptide (50).

In a separate study of type 1 diabetic patients, complete loss of β-cell function (loss of C-peptide response to oral glucose) was also associated with early progression to preproliferative retinopathy (51). A population-based study found that glycemic control and C-peptide (assessed on random sampling) were related to the incidence and progression of retinopathy, although glycemic control was the most important factor (52). Prevention of progression toward full exhaustion of β-cells and consequent dependency on insulin could be applied not only to LADA patients but also to nondiabetic offspring of probands with LADA because they may show impaired insulin secretion (53). When designing a preventative strategy, however, a number of problems may arise. Thus, studies available in patients with LADA greatly differ in terms of definition of selected patients, distance from diagnosis of hyperglycemia, inclusion criteria, and, last but not least, the fact that different populations (Caucasians, Hispanic-Americans, African-Americans, Indians, and Asians) have been investigated. The latter finding is of particular relevance because different HLA genotypes in these populations may influence progression toward insulin dependency. Above all, the age at diagnosis of hyperglycemia and the time elapsed between diagnosis and when the patient is found to be GAD/

ICA/IA2 antibody–positive strongly influence the management of these patients.

For patients in whom the primary defect is loss of β-cell function, treatment should logically aim to restore β-cell mass or function. Prevention of progression toward insulin dependency in LADA patients has raised considerable interest (54). At present, such treatment might include the use of SUs or insulin. Whereas insulin therapy could be valuable in maintaining β-cell function, it would be unusual to treat with insulin in a study aiming to alter the risk of progression to insulin treatment and dependency. SUs are already used extensively in non–insulin-requiring diabetic patients and although their efficacy has not been formally tested, it is evident that their use has not arrested the progression to insulin dependency. In patients with LADA, insulin resistance can coexist, and metformin, which was successfully used in obese type 2 diabetic patients without knowledge of whether patients were GAD antibody–positive (55), might be beneficial.

There is no doubt that clinical trials are needed in patients with LADA to identify the proper therapeutic strategy for controlling hyperglycemia. Careful selection of patients, taking into account duration of overt hyperglycemia and age, is crucial. The calculation of the required sample size would not be easy depending on the end points of the study. The data from the UKPDS (35) and a recent publication aiming to predict the time required between diagnosis of LADA and the need for insulin by measuring ICA and GAD antibodies (56) may help in calculating the sample size. The antibody titer is also important because low antibody titer may signify a less aggressive β-cell autoimmunity and slower progression to insulin therapy, as recently reported (57).

A number of attractive therapeutic possibilities are available for preventing progression toward insulin dependency in LADA patients, ranging from antigen-based therapies to monoclonal antibody– and cytokine-based therapies; such approaches are under consideration for preventing the development of type 1 diabetes in the young.

Glitazones

The use of glitazones, although recently introduced in the management of type 2 diabetic patients, may be of potential interest in patients with LADA. This new class of oral antidiabetic agents has its primary effect on peripheral insulin action (58). The glitazones have the potential to preserve endogenous insulin secretory reserve, and from many of the models studied, improvement in glucose metabolism is accompanied by a reduction in circulating insulin concentration (59). There is interesting evidence that glitazones increase insulin synthesis and the insulin content of islet cells as well as improve the secretory response of islets (60). In addition to its hypoglycemic effect, troglitazone has been shown to possess in vitro anti-inflammatory properties, as shown by the reduction of cytokines such as tumor necrosis factor-α and γ-interferon (61). The latter mechanism could explain why, in the experimental model of the NOD mouse, troglitazone protects animals from diabetes development (62). Also, another compound of the same family of drugs—rosiglitazone—has been shown to possess similar effects in reducing diabetes incidence of autoimmune diabetes (63). As in the case of metformin, the absence of any direct effect on stimulation of insulin secretion by glitazones in achieving normalization of blood glucose could be of benefit in LADA patients. We can conclude that this new class of compounds could in theory be the most appropriate therapy for hyperglycemia in LADA patients. However, only a clinical trial can prove it.

Insulin

Early intervention with insulin may be protective to the β-cells, the rationale being the β-cell rest and reduction in antigen exposure associated with insulin output (64). The insulin approach is currently used in the Diabetes Prevention Trial—Type 1 Diabetes (DPT-1) for secondary prevention of type 1 diabetes (65). A pilot trial comparing insulin versus SUs in LADA patients was carried out in Japan and focused on evaluating the effect on C-peptide secretion (66). Results were encouraging, showing that insulin-treated patients maintain higher β-cell function than SU-treated patients. In the context of LADA, in which the process of β-cell destruction is thought to be slow progressing (4), the use of insulin could indeed be beneficial to protect the β-cell mass; however, only a properly designed trial can offer definitive data on this issue. Nevertheless, from a practical point of view, it should be underlined that patients reluctantly accept insulin injections, especially if their blood glucose levels are initially moderately increased and, as such, this may limit insulin from being used very early after diabetes diagnosis in GAD-positive patients with clinical features of type 2 diabetic patients. The recently reported inhaled insulin in patients with type 1 diabetes would be an interesting option to test in LADA patients (67).

In our view, an appropriate treatment of hyperglycemia in LADA patients would be worthwhile if it beneficially influences metabolic control or changes the natural history of the disease (e.g., preventing the destruction of β-cells).

The recent introduction in phase II trials of vaccine-based therapy (Diapep 277 in patients with recent-onset type 1 diabetes) (68) may offer useful information for applying the same approach to LADA patients with the aim of protecting β-cell function. In the case of LADA, however, insulin resistance often associated with this condition (19) should also be tackled. A prevention trial should aim to stop progression to insulin dependency. The screening involved in setting up a clinical trial should not be difficult, with clinical end points being represented by the introduction of insulin therapy as the primary end point and insulin response to an intravenous glucose tolerance test and deterioration of C-peptide secretion as secondary end points. However, loss of C-peptide may not be so easy to use as a secondary end point, especially if a preventative trial includes patients with only one autoantibody and age >55 years.

In conclusion, patients with LADA are an ideal group in which to test measures that, if successful, may be applied to prevent insulin dependency in individuals of younger age who are susceptible to type 1 diabetes.

Acknowledgments— Work in the laboratory of the authors was supported by grants from the Italian Ministry of University and Scientific Research, the Diabetes Endocrinology and Metabolism Foundation, the Centro Internazionale Studi Diabete Foundation, and the Juvenile Diabetes Foundation International.

The authors thank Dr. Mark Airey, Prof. Rys Williams, and Prof. David Leslie for suggestions and collaboration in this review. Jessica Williams is acknowledged for her work in the final preparation of the manuscript.

References

1. Alberti KG, Zimmet PZ, for the WHO Consultation: Definition, diagnosis and classification of diabetes mellitus and its complications. I. Diagnosis and classification of diabetes mellitus: provisional report of a WHO Consultation. *Diabet Med* 15:539–553, 1998
2. Schiel A, Müller UA: GAD autoantibodies in a selection-free population of insulin-treated diabetic patients: indicator of a high prevalence of LADA? *Diabetes Res Clin Pract* 49:33–40, 2000
3. Tuomi T, Groop LC, Zimmet PZ, Rowley MJ, Knowles W, Mackay IR: Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease. *Diabetes* 42:359–362, 1993
4. Zimmet P, Turner R, McCarty D, Rowley M, Mackay I: Crucial points at diagnosis: type 2 diabetes or slow type 1 diabetes. *Diabetes Care* 22:59–64, 1999
5. Palmer JP, Juneja R: Type 1 ½ diabetes: myth or reality? *Autoimmunity* 29:65–83, 1999
6. Horton V, Stratton I, Bottazzo GF, Shattock M, Mckay I, Zimmet P, Manley S, Holman R, Turner R: Genetic heterogeneity of autoimmune diabetes: age of presentation in adults is influenced by HLA DRB1 and DQB1 genotypes (UKPDS 43): UK Prospective Diabetes Study (UKPDS) Group. *Diabetologia* 42:608–616, 1999
7. Akerblom HK, Knip M: Putative environmental factors in type 1 diabetes. *Diabete Metab Rev* 14:31–67, 1999
8. Shimada A, Imazu Y, Morinaga S, Funae O, Kasuga A, Atsumi Y: T-cell insulitis found in anti-GAD65+ diabetes with residual function: a case report. *Diabetes Care* 22:615–617, 1999
9. Seissler J, Schott M, Steinbrenner R, Peterson P, Scherbaum WA: Autoantibodies adrenal cytochrome P450 antigens in isolated Addison's disease autoimmune polyendocrine syndrome type II. *Exp Clin Endocrinol Diabetes* 107:208–213, 1999
10. Komulainen J, Kulmala P, Savola K, Lounamaa R, Ilonen J, Reijonen H, Knip M, Akerblom HK: Clinical, autoimmune, and genetic characteristics of very young children with type 1 diabetes: Childhood Diabetes in Finland (DiMe) Study Group. *Diabetes Care* 22:1950–1955, 1999
11. Pozzilli P, Visalli N, Buzzetti R, Cavallo MG, Marietti G, Hawa M, Leslie RDG: Metabolic and immune parameters at clinical onset of insulin-dependent diabetes: a population-based study. *Metabolism* 10:1205–1210, 1998
12. Caillat-Zucman S, Garchon HJ, Timsit J, Assan R, Boitard C, Djilali-Saiah I, Bougneres P, Bach JF: Age-dependent HLA genetic heterogeneity of type 1 insulin-dependent diabetes mellitus. *J Clin Invest* 90:2242–2250, 1992
13. Vandewalle CL, Decraene T, Schuit FC, De Leeuw IH, Pipeleers DG, Gorus FK: Insulin autoantibodies and high titre islet cell antibodies are preferentially associated with the HLA DQA1*0301-DQB1*0302 haplotype at clinical type 1 (insulin-dependent) diabetes mellitus before age 10 years, but not at onset between 10 and 40 years: The Belgian Diabetes Registry. *Diabetologia* 36:1155–1162, 1993
14. Hawa NU, Fava D, Medici F, Deng YJ, Notkins AL, De Mattia G, Leslie RDG: Antibodies to IA-2 and GAD65 in type 1 and type 2 diabetes. *Diabetes Care* 23:228–233, 2000
15. Niskanen LK, Tuomi T, Karjaiainen J, Groop LC, Uusitupa MI: GAD antibodies in NIDDM: ten-year follow-up from the diagnosis. *Diabetes Care* 18:1557–1565, 1995
16. Gottsäter A, Sarnueisson U, Nilsson S, Lernmark Ä, Sundkvist G: Islet cell antibodies and fasting plasma C-peptide during the first 10 years after diagnosis in patients with diabetes mellitus diagnosed in adult age. *Diabetes Nut Met* 5:243–248, 1992
17. Leslie RD, Pozzilli P: Type 1 diabetes masquerading as type 2 diabetes: possible implications for prevention and treatment. *Diabetes Care* 17:1214–1219, 1994
18. Seissler J, de Sonnaville JJ, Morgenthaler NG, Steinbrenner H, Glawe D, Khoo-Morgenthaler UY, Lan MS, Notkins AL, Heine RJ, Scherbaum WA: Immunological heterogeneity in type 1 diabetes: presence of autoantibody patterns in patients with acute onset and slowly progressive disease. *Diabetologia* 41:891–897, 1998
19. Carlsson A, Sundkvist G, Groop L, Tuomi T: Insulin and glucagon secretion in patients with slowly progressing autoimmune diabetes (LADA). *J Clin Endocrinol Metab* 85:76–80, 2000
20. Di Mario U, Irvine WJ, Borsey DQ, Kyner JL, Weston J, Galfo C: Immune abnormalities in diabetic patients not requiring insulin at diagnosis. *Diabetologia* 25:392–395, 1983
21. Gottsäter A, Landin-Olsson M, Fernlund P, Lernmark Ä, Sundkvist G: β-Cell function in relation to islet cell antibodies during the first 3 years after clinical diagnosis of diabetes in type II diabetic patients. *Diabetes Care* 16:902–910, 1993
22. Kobayashi T, Tamemoto K, Nakanishi K, Kato N, Okubo M, Kajio H, Sugimoto T, Murase T, Kosaka K: Immunogenetic and clinical characterization of slowly progressive IDDM. *Diabetes Care* 16:780–788, 1993
23. Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A, Nissén M, Ehmström B, Forsén B, Snickars B, Lahti K, Forsblom C, Saloranta C, Taskinen MR, Groop LC: Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. *Diabetes* 48:150–157, 1999
24. Bosi EP, Garancini NT, Poggiali F, Bonifacio E, Gallus G: Low prevalence of islet autoimmunity in adult diabetes and low predictive value of islet autoantibodies in the general adult population of northern Italy. *Diabetologia* 42:840–844, 1999
25. EURODIAB ACE Study Group: Variation and trends in incidence of childhood diabetes in Europe. *Lancet* 355:873–876, 2000
26. Medici F, Hawa MI, Giorgini A, Panelo A, Solfelix CM, Leslie RD, Pozzilli P: Antibodies to GAD65 and a tyrosine phosphatase-like molecule IA-2ic in Filipino type 1 diabetic patients. *Diabetes Care* 22: 1458–1463, 1999
27. Banerji MI, Chaiken RL, Huey H, Tuomi T, Norin AJ, Mackay IR, Rowley MJ, Zimmet PZ, Lebovitz HE: GAD antibody negative NIDDM in black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. *Diabetes* 43:741–745, 1994
28. Dowse GK, Zimmet PZ, Spark RA, Mavo B, Rowley MJ, Mackay IR: Lack of antibodies to glutamic acid decarboxylase in young adults of the high diabetes prevalence Wanigela people of Papua New Guinea. *Diabetes Res Clin Pract* 24:195–198, 1994
29. Thai AC, Ng WY, Loke KY, Lee WR, Lui KF, Cheah JS: Anti-GAD antibodies in Chinese patients with youth and adult-onset IDDM and NIDDM. *Diabetologia* 40: 1425–1430, 1997
30. Kasuga A, Maruyama T, Ozawa Y, Takei I, Falorni A, Lernmark Ä, Saruta T: Antibody to the M(r) 65,000 isoform of glutamic acid decarboxylase are detected in non-insulin-dependent diabetes in Japanese. *J Autoimmun* 9:105–111, 1996
31. Gottsäter A, Landin-Olsson M, Lernmark Ä, Ferlund P, Sundkvist G, Hagopian WA: Glutamate decarboxylase antibody levels predict rate of beta-cell decline in adult-onset diabetes. *Diabetes Res Clin Pract* 27:133–140, 1995
32. Wroblewski M, Gottsäter A, Lindgarde F, Fernlund P, Sundkvist G: Gender, autoantibodies, and obesity in newly diagnosed diabetic patients aged 40–75 years. *Diabetes Care* 21:250–255, 1998
33. Ruige JB, Batstra MR, Aanstoot H-J, Bouter LM, Bruining GJ, De Neeling JN, Heine RJ: Low prevalence of antibodies to GAD65 in a 50- to 74-year-old general Dutch population: The Hoorn Study. *Diabetes Care* 20:1108–1110, 1997
34. Bruno G, De Salvia A, Arcari R, Borra M, Grosso N, Carta Q, Trovati M, Veglio M, Pagano G: Clinical, immunological, and

genetic heterogenity of diabetes in an Italian population-based cohort of lean newly diagnosed patients aged 30–54 years. *Diabetes Care* 22:50–55, 1999
35. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, Shattock M, Bottazzo GF, Holman R, for UK Prospective Diabetes Study (UKPDS) Group: UKPDS 25: Autoantibodies to islet cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. *Lancet* 350:1288–1293, 1997
36. Pietropaolo M, Barinas-Mitchell E, Pietropaolo SL, Kuller LH, Trucco M: Evidence of islet cell autoimmunity in elderly patients with type 2 diabetes. *Diabetes* 49: 32–38, 2000
37. Buzzetti R, Quattrocchi CC, Nisticò L: Dissecting the genetics of type 1 diabetes: relevance for familial clustering and differences in incidence. *Diabete Metab Rev* 14:111–128, 1998
38. Svejgaard A, Jakobsen BK, Platz P, Ryder LP, Nerup J, Christy M, Borch-Johnsen K, Parving H, Deckert T, Mølsted-Pedersen L, Kühl C, Buschard K, Green A: HLA associations in insulin-dependent diabetes: search for heterogeneity in different groups of patients from a homogeneous population. *Tissue Antigens* 28:237–244, 1986
39. Karjalainen J, Salmela P, Ilonen J, Surcel HM, Knip M: A comparison of childhood and adult type 1 diabetes mellitus. *N Engl J Med* 320:881–886, 1989
40. Lohmann T, Seissler J, Verlohren H, Schröder A, Rötger J, Dähn K, Morgenthaler N, Scherbaum WA: Distinct genetic and immunological features in patients with onset of IDDM before and after age 40. *Diabetes Care* 20:524–529, 1997
41. Gambelunghe G, Forini F, Laureti S, Murdolo G, Toraldo G, Santeusanio F, Brunetti P, Sanjeevi CB, Falorni A: Increased risk for endocrine autoimmunity in Italian type 2 diabetic patients with GAD 65 autoantibodies. *Clin Endocrinol* 52:565–573, 2000
42. Isomaa B, Almgren P, Henricsson M, Taskinen MR, Tuomi T, Groop L, Sarelin L: Chronic complications in patients with slowly progressing autoimmune type 1 diabetes (LADA). *Diabetes Care* 22:1347–1353, 1999
43. Gerich JE: Oral hyperglycaemic agents. *N Engl J Med* 321:1231–1242, 1989
44. Di Mario U, Dotta F: Modulation of antigen expression in relation to intervention strategies in type 1 diabetes. *Diabete Metab Rev* 9:245–249, 1993
45. DeFronzo RA, Goodman AM, the Multicenter Metformin Study Group: Efficacy of metformin in patients with non-insulin dependent diabetes mellitus. *N Engl J Med* 333:541–549, 1995
46. Johansen K: Efficacy of metformin in the treatment of NIDDM: meta-analysis. *Diabetes Care* 22:33–37, 1999
47. Beales PE, Giorgini A, Annovazzi A, Signore A, Parlapiano C, Pozzilli P: Metformin does not alter diabetes incidence in the NOD mouse. *Horm Metab Res* 29: 261–263, 1997
48. Decochez K, Keymeulen B, Somers G, Dorchy G, De Leeuw IH, Mathieu C, Rottiers R, Winnock F, ver Elst K, Weets I, Kaufman L, Pipeleers DG, Rottiers R: Use of an islet cell antibody assay to identify type 1 diabetic patients with rapid decrease in C-peptide levels after clinical onset: Belgian Diabetes Registry. *Diabetes Care* 23:1072–1078, 2000
49. Pozzilli P, Browne PD, Kolb H, the Nicotinamide Trialists: Meta-analysis of nicotinamide treatment in patients with recent onset insulin dependent diabetes. *Diabetes Care* 19:1357–1363, 1996
50. Sjoberg S, Gunnarsson R, Gjotterberg M, Lefvert AK, Persson A, Ostman J: Residual insulin production, glycaemic control and prevalence of microvascular lesions and polyneuropathy in long-term type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 30:208–213, 1987
51. Klein R, Klein BE, Moss SE: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XVI. The relationship of C-peptide to the incidence and progression of diabetic retinopathy. *Diabetes* 44:796–801, 1995
52. Nakanishi K, Kobayashi T, Inoko R, Tsuji K, Murase T, Kosaka K: Residual β-cell function and HLA-A24 in IDDM: markers of glycemic control and subsequent development of diabetic retinopathy. *Diabetes* 44:1334–1339, 1995
53. Vauhkonen I, Niskanen L, Knip M, Ilonen J, Vanninen E, Kainulainen S, Uusitupa M, Laakso M: Impaired insulin secretion in non-diabetic offspring of probands with latent autoimmune diabetes mellitus in adults. *Diabetologia* 43:69–78, 2000
54. Zimmet PZ: The pathogenesis and prevention of diabetes in adults: genes, autoimmunity, and demography. *Diabetes Care* 18:1050–1064, 1995
55. Pagano G, Tagliaferro V, Carta Q, Caselle MT, Bozzo C, Vitelli F, Trovati M, Cocuzza E: Metformin reduces insulin requirement on type 1 (insulin-dependent) diabetes. *Diabetologia* 24:351–354, 1983
56. Littorin B, Sundkvist G, Hagopian W, Landin-Olsson M, Lernmark Ä, Ostman J, Arnqvist HI, Blohme G, Bolinder J, Eriksson JW, Lithner F, Schersten B, Wibell L: Islet cell and glutamic acid decarbloxylase antibodies present at diagnosis of diabetes predict the need for insulin treatment: a cohort study in young adults whose disease was initially labeled as type 2 or unclassifiable diabetes. *Diabetes Care* 22: 409–412, 1999
57. Schranz DB, Bekris L, Landin-Olsson M, Torn C, Nilang A, Toll A, Sjostrom J, Gronlund H, Lernmark Ä: Newly diagnosed latent autoimmune diabetes in adults (LADA) is associated with low level glutamate decarboxylase (GAD65) and IA-2 autoantibodies: Diabetes Incidence Study in Sweden (DISS). *Horm Metab Res* 32:133–138, 2000
58. Henry RR: Thiazolidinediones. *Endocrinol Met Clinics North Am* 26:553–573, 1997
59. Prigeon RL, Kahn SE, Porte D Jr: Effect of troglitazone on β cell function, insulin sensitivity, and glycemic control in subjects with type 2 diabetes mellitus. *Clin Endocrinol Metab* 83:819–823, 1998
60. Masuda K, Okamoto Y, Tsuura Y, Kato S, Misura T, Tsuda K, Horikoshi H, Ishida H, Seino Y: Effects of troglitazone (CS-045) on insulin secretion in isolated rat pancreatic cells and HIT cells: an insulinotropic mechanism distinct from glibenclamide. *Diabetologia* 38:24–30, 1995
61. Giorgini A, Beales P, Mire-Sluis A, Scott D, Liddi R, Pozzilli P: Troglitazone exhibits immunomodulatory activity on the cytokine production of activated human lymphocytes. *Horm Metab Res* 31:1–4, 1999
62. Beales PE, Liddi R, Giorgini A, Signore A, Procaccini E, Batchelor K, Pozzilli P: Troglitazone prevents insulin dependent diabetes in the non-obese diabetic mouse. *Eur J Pharmacol* 357:221–225, 1998
63. Beales PE, Rosignoli G, Liddi R, Batchelor K, Pozzilli P: Rosiglitazone reduces diabetes incidence in the NOD mouse (Abstract). *Diabetes Res Clin Pract* 50 (Suppl. 1):1518, 2000
64. Atkinson MA, Maclaren NK, Luchetta R: Insulitis and diabetes in NOD mice reduced by prophylactic insulin therapy. *Diabetes* 39:933–937, 1990
65. Steffes MW: The Diabetes Prevention Trial-Type 1 diabetes (DPT-l): implementation of screening and staging of relatives: DPT-1 Study Group. *Transplant Proc* 27: 3377–3381, 1995
66. Kobayashi T, Nakanishi K, Murase T, Kosaka K: Small doses of subcutaneous insulin as a strategy for preventing slowly progressive β-cell failure in islet cell antibody-positive patients with clinical features of NIDDM. *Diabetes* 45:622–626, 1996
67. Skyler JS, Cefalu WT, Kourides IA, Landschultz WH, Balagtas CC, Cheng S-L, Gelfand RA: Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. *Lancet* 357:331–335, 2001
68. Elias D, Metzger M, Avron A, Tamir M, Yosefberg Z, Philip M, Raz I: C-peptide preservation and TH1 to TH2 shift in type 1 diabetes patients vaccinated with Diapep277 (Abstract). *Diabet Metab Res Rev* 17 (Suppl. 1):S39, 2001