Latent Autoimmune Diabetes in Adults

Definition, Prevalence, β-Cell Function, and Treatment

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Latent autoimmune diabetes in adults (LADA) is a disorder in which, despite the presence of islet antibodies at diagnosis of diabetes, the progression of autoimmune β-cell failure is slow. LADA patients are therefore not insulin requiring, at least during the first 6 months after diagnosis of diabetes. Among patients with phenotypic type 2 diabetes, LADA occurs in 10% of individuals older than 35 years and in 25% below that age. Prospective studies of β-cell function show that LADA patients with multiple islet antibodies develop β-cell failure within 5 years, whereas those with only GAD antibodies (GADAs) or only islet cell antibodies (ICAs) mostly develop β-cell failure after 5 years. Even though it may take up to 12 years until β-cell failure occurs in some patients, impairments in the β-cell response to intravenous glucose and glucagon can be detected at diagnosis of diabetes. Consequently, LADA is not a latent disease; therefore, autoimmune diabetes in adults with slowly progressive β-cell failure might be a more adequate concept. In agreement with proved impaired β-cell function at diagnosis of diabetes, insulin is the treatment of choice.
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In 1986, Groop et al. (1) reported a subgroup of type 2 diabetic patients who, despite having islet autoantibodies, showed preserved β-cell function. The type of diabetes in these patients was referred to as latent type 1 diabetes, showing clearly different features from classic type 1 and classic type 2 diabetes. Later, Tuomi et al. (2) and Zimmet et al. (3) launched the eponym LADA (latent autoimmune diabetes in adults) for this slowly progressive form of autoimmune diabetes initially managed with diet and oral hypoglycemic agents before becoming insulin requiring. However, it is now clear that classic autoimmune type 1 diabetes (4) is frequent among patients older than 30 years at diagnosis of diabetes. Whether LADA is a separate entity from conventional autoimmune type 1 diabetes among adults may therefore be challenged. In this article, we review LADA with regard to definitions and our experience with β-cell function and discuss treatment. The question as to whether the eponym LADA still should be used will also be considered.

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ADA, autoimmune diabetes in adults; GADA, GAD antibody; IA-2A; IA-2 antibody; ICA, islet cell antibody; LADA, latent autoimmune diabetes in adults.

DEFINITION AND PREVALENCE

LADA is the most common term describing patients with a type 2 diabetic phenotype combined with islet antibodies and slowly progressive β-cell failure. However, other eponyms are shown in Table 1. If defined as a type 2 diabetic phenotype combined with islet antibodies, the prevalence of LADA is around 10% among incident case subjects of diabetes aged 40–75 years (16). A similar prevalence is found among non-insulin-requiring patients older than 35 years at diagnosis with phenotypic type 2 diabetes (17). Actually, a similar frequency of LADA (~10%) was found among type 2 diabetic patients of all ages in the U.K. Prospective Diabetes Study (18). Among type 2 diabetic patients younger than 35 years of age at diagnosis, the frequency of LADA is much higher (~25%) (18–20). Although LADA patients by definition are not insulin requiring at and during the first time after diagnosis of diabetes, within 6 years, β-cell function is severely impaired, leading to insulin dependency in most LADA patients (18,21). Nevertheless, β-cell failure, defined as unmeasurable fasting C-peptide, may take up to 12 years until it occurs in patients with islet antibodies (22). It is important to clarify that obesity does not exclude LADA. Obese type 2–like diabetic patients with islet antibodies show progressive β-cell failure (23). In agreement, Juneja et al. found that only islet antibodies (islet cell antibodies [ICAs] or GAD antibodies [GADAs]) defined "LADA" (≈ type 1 1/2 diabetes); not BMI, age, or clinical presentation (24). High concentrations of islet antibodies (12) predict future β-cell failure, whereas a low number of islet antibodies, particularly lack of ICAs, is associated with lack of progression to β-cell failure (25,26). Although LADA is considered to be confined to adulthood, Lohmann et al. (9) recently introduced the term "LADY-like" (latent autoimmune diabetes in the young) based on two children diagnosed with islet antibodies without insulin dependency, who later showed slowly progressive β-cell failure. A similar observation in a Turkish case (15) gave birth to another eponym: LADC (latent autoimmune diabetes in children). The rising prevalence of obesity among children indicates that assessment for islet antibodies will be increasingly important. Without determination of islet antibodies, it is not possible to separate type 1 diabetes from type 2 diabetes among obese children. Slowly progressive autoimmune diabetes is a growing problem in children.

To distinguish LADA from classic type 1 diabetes, HLA studies may be of value. Although it has been suggested that LADA deviates from classic type 1 diabetes (17), others have found classic type 1 diabetes risk HLA genotypes in LADA (13,27). Indeed, low frequencies of type 1

TABLE 1
Eponyms for autoimmune diabetes in adults

Eponym	Reference
Latent type 1 diabetes	1
Latent autoimmune diabetes in adults (LADA)	2
Slowly progressive IDDM (SPIDDM)	5
Slow-onset IDDM	6
Slowly progressive type 1 diabetes	7
Type 1 1/2 diabetes	8
LADY-like	9
Autoimmune diabetes not requiring insulin at diagnosis	10
LADA–type 1 and –type 2	11
Slowly progressive β-cell failure	12
Slowly progressive adult-onset type 1 diabetes	13
Antibody-positive phenotypic type 2 diabetes with obesity	14
Latent autoimmune diabetes in children (LADC)	15

diabetes protective HLA genotypes, particularly HLA DQA1-DQB1*0102(3)-*0602(3)/X, are associated with LADA (27). It has been claimed that there might be a co-segregation between type 1 and type 2 diabetes in the context of LADA (28). An assumption that LADA may be a feature of a general autoimmune tendency has support from an increased frequency of serological markers of thyroid and adrenal disease in type 2 diabetic patients with GADAs (29). Antibodies associated with celiac disease are also found more often in LADA patients than in type 2 diabetic patients (30). However, these antibodies are also more frequent than expected in classic type 1 diabetic patient and thereby cannot be used to separate LADA from classic type 1 diabetes.

Most recently, the eponym ADA (autoimmune diabetes in adults) has been suggested to replace the term LADA for diabetic patients with islet antibodies without a need for insulin treatment for at least the first 6 months after diagnosis (31). ADA is meant to distinguish slowly progressive autoimmune diabetes from the classic rapid onset autoimmune type 1 diabetes.

β-CELL FUNCTION IN (L)ADA

To follow the development of β-cell dysfunction in patients with the type 2 diabetic phenotype combined with islet antibodies, we prospectively followed 233 adult-onset diabetic patients after their diagnosis of diabetes since 1985–1987 (32). Among these patients, 22 ICA^+ and 17 ICA^- were regularly followed with a combined intravenous glucose and glucagon test (33) during the first 5 years after diagnosis. We followed the remaining patients by fasting plasma (p)-C-peptide measurements. Here, we summarize the most pertinent data collected (22,34).

At baseline soon after diagnosis, the plasma C-peptide response to the glucose infusion was clearly lower ($P < 0.001$) in type 2 diabetic patients with ICAs compared with type 2 diabetic patients without ICAs (Fig. 1*A*). However, the plasma C-peptide response to glucose was significantly ($P < 0.05$) higher in ICA^+ type 2 diabetic patients versus patients with classic type 1 diabetes. One year after diagnosis, the plasma C-peptide response to glucose infusion had deteriorated in ICA^+ type 2 diabetic patients, now no different from the response found among our classic type 1 diabetic patients. The plasma C-peptide response to glucagon injection at diagnosis was as impaired in type 2 diabetic patients with ICAs as in classic type 1 diabetes (Fig. 1*B*), in both groups clearly ($P < 0.01$) lower than in ICA^- type 2 diabetic patients. Similarly, at diagnosis, fasting plasma C-peptide concentrations were as low among type 2 diabetic patients with ICAs as among classic type 1 diabetic patients (Fig. 2). Hence, there was an impairment of β-cell function initially in ICA^+ type 2 diabetic patients, although less severe than in classic type 1 diabetes (34). Three years after diagnosis, fasting plasma C-peptide had clearly decreased both in ICA^+ type 2 diabetic patients and in patients with classic type 1 diabetes.

Figure 3 illustrates the development of the plasma

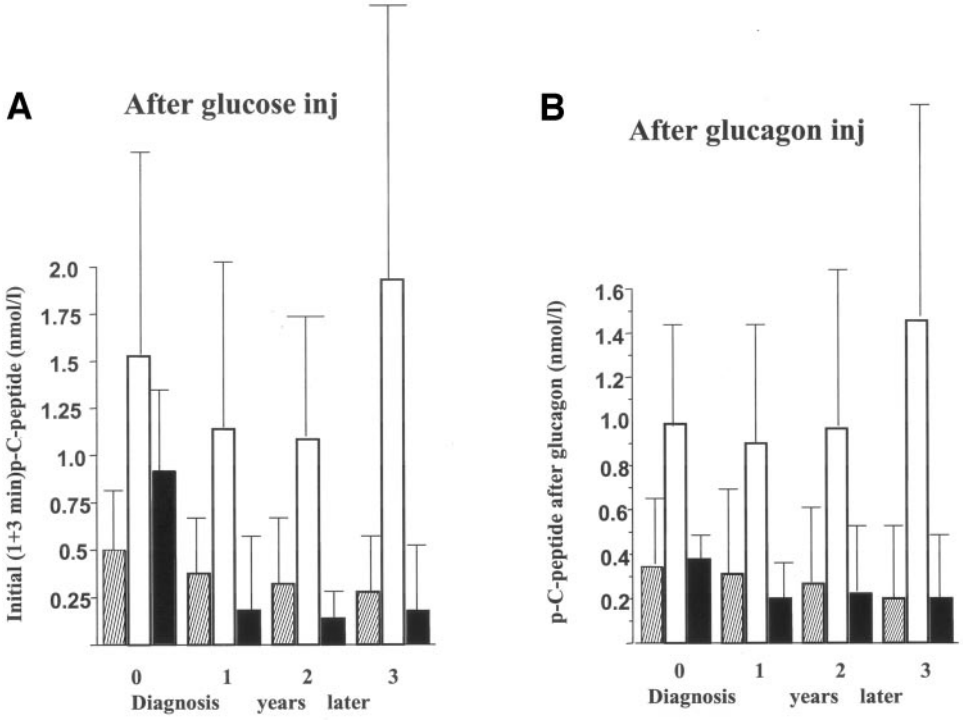

FIG. 1. A combined intravenous glucose and glucagon test conducted at diagnosis and 1, 2, and 3 years after diagnosis in newly diagnosed type 1 diabetic patients (n = 17, ▨), type 2 diabetic patients without ICAs (n = 10, □), and type 2 diabetic patients with ICAs (n = 11, ■). At diagnosis, the initial 1 + 3 min plasma (p-)C-peptide response to glucose (*A*) in type 2 diabetic patients with ICAs was intermediate between the responses found in type 2 diabetic patients without ICAs and patients with classic type 1 diabetes. After the first year, however, this response had deteriorated in type 2 diabetic patients with ICAs and now did not differ versus patients with classic type 1 diabetes. On the other hand, at diagnosis, the plasma C-peptide response to glucagon (*B*) was as low in type 2 diabetic patients with ICAs as in classic type 1 diabetic patients. Bars indicate the mean and horizontal lines indicate SD. inj, injection.

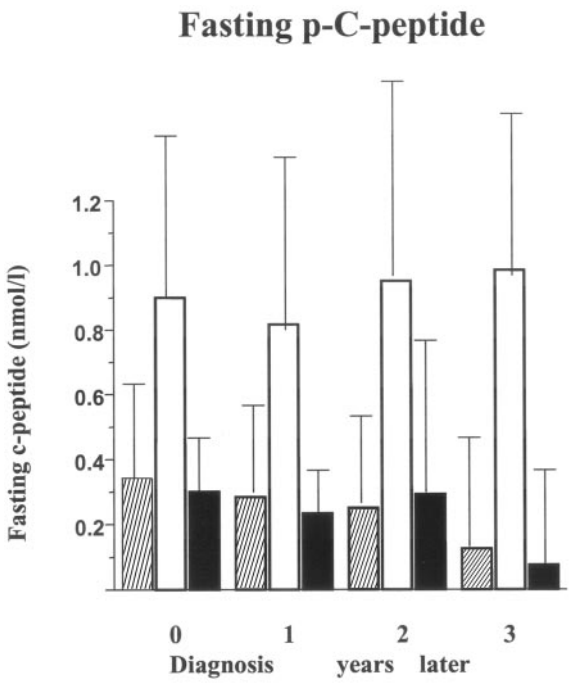

FIG. 2. Fasting plasma (p-)C-peptide at diagnosis and 1, 2, and 3 years after diagnosis in newly diagnosed type 1 diabetic patients (n = 17, ▨), type 2 diabetic patients without ICAs (n = 10, □), and type 2 diabetic patients with ICAs (n = 11, ■). At diagnosis, fasting plasma C-peptide was as low in type 2 diabetic patients with ICAs as in type 1 diabetic patients. Bars indicate the mean and horizontal lines indicate SD.

C-peptide responses to the combined glucose and glucagon provocation test from diagnosis up to 5–7 years thereafter among patients with islet antibodies (GADAs and IA-2 antibodies [IA-2As] now also considered) and control subjects. Adult-onset diabetic patients with islet antibodies showed a low response of plasma C-peptide to the glucose injection at diagnosis. Indeed, this was also shown among diabetic patients without islet antibodies. Moreover, the plasma C-peptide response to the glucagon

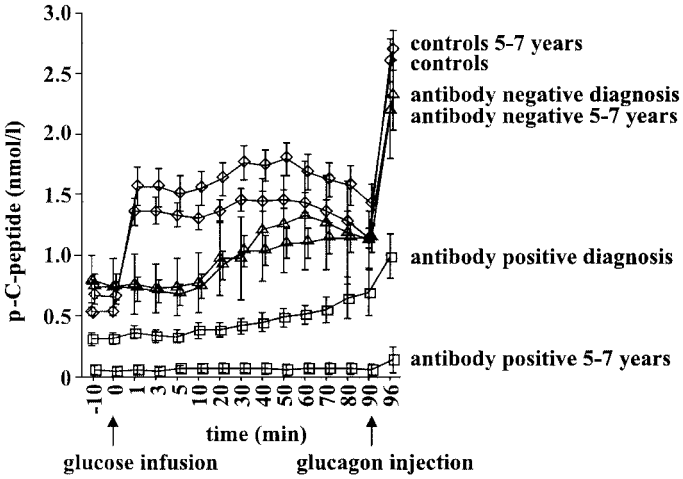

FIG. 3. The development of plasma (p-)C-peptide responses to an intravenous glucose (0.5 g glucose/kg body wt) and glucagon (1 mg) infusion test up to 5–7 years after diagnosis among adult-onset diabetic patients. Symbols indicate the mean and horizontal lines indicate SE. At diagnosis, patients with islet antibodies showed a lower mean increment in plasma C-peptide to glucagon compared with patients lacking antibodies and control subjects. Five to seven years later, the response of plasma C-peptide to glucagon had vanished among diabetic patients with islet antibodies.

injection was clearly diminished among patients with islet antibodies compared with those without at the time of diagnosis and had further deteriorated among the former 5–7 years after diagnosis. Hence, though not as severe as in classic type 1 diabetic patients, LADA patients have an early impairment in β-cell function. LADA is not a latent form of autoimmune diabetes. Hence, we favor the use of ADA (31) rather than LADA for this type of patient in the future.

The complete patient group was followed up 12 years after diagnosis of diabetes (22). Figure 4 summarizes the major results. Adult-onset diabetic patients with two or three antibodies (ICAs, GADAs, IA-2As) deteriorated in β-cell function within 5 years, whereas among those with only ICAs or only GADAs, severe β-cell dysfunction seemed to occur later, as noted at the follow-up after 12 years. In contrast, β-cell function was unaffected and preserved 12 years after diagnosis among individuals without islet antibodies and individuals with only IA-2As. Interestingly, five diabetic patients initially without islet antibodies developed ICAs after diagnosis of diabetes, and actually, after becoming ICA^+, their fasting C-peptide concentrations decreased. Hence, our 12-year prospective study of patients with adult-onset diabetes showed that the presence of two or three islet antibodies (ICAs, GADAs, and IA-2As) at diagnosis predicts severe deterioration in β-cell function within 5 years. The presence of only ICAs or only GADAs is associated with severe deterioration within 12 years, whereas a development of ICAs after diagnosis predicts a later development of β-cell dysfunction.

Whether the responses of β-cells to oral glucose or mixed meals are as impaired as the responses to intravenous glucose or glucagon are unknown. No comparison between oral versus intravenous responses of insulin secretion in LADA patients has been published (31).

TREATMENT OF LADA

General. Diet treatment in LADA is similar to that in classic type 1 diabetes. Obese LADA patients benefit from restriction in calories consumed and increased levels of physical activity. A warning message has been issued for glibenclamide, which might promote the autoimmune process (35). Thiazolidinediones seem to prevent diabetes in the nonobese diabetic (NOD) mouse (36). However, human data are lacking. Metformin is probably useful in obese LADA patients. Nevertheless, insulin therapy is the treatment of choice. As indicated from our studies, β-cell function is impaired at diagnosis of autoimmune diabetes in adult patients, irrespective of the clinical phenotype. Hence, there is no reason to postpone the commencement of insulin therapy. Indeed, type 2 diabetic patients without islet antibodies primarily treated with insulin demonstrate better β-cell function 2 years after diagnosis than those primarily treated with glibenclamide (37). Primarily insulin-treated type 2 diabetic patients also show better glycemic control (lower HbA_{1c} [A1C] values) 2 (37) and 4 years (38) after diagnosis than their glibenclamide-treated counterparts. This emphasizes that patients with autoimmune diabetes should be insulin-treated as early as possible.

Experimental treatment to prevent progression of β-cell destruction. Kobayashi et al. (39) identified three independent risk factors for progression of β-cell failure in LADA: sulfonylurea treatment, ICA^+ periods, and initial body weight. In their pilot study, a small dose of insulin

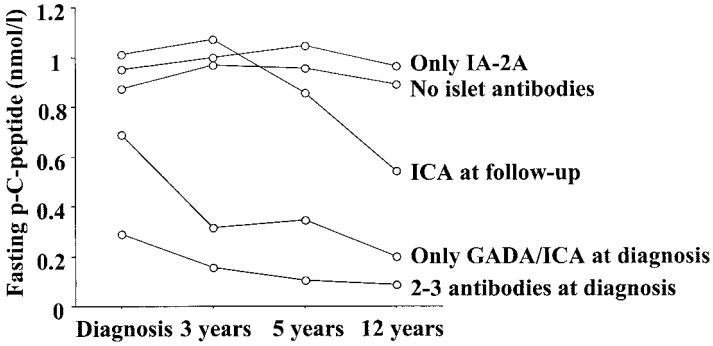

FIG. 4. Fasting plasma (p-)C-peptide concentrations during the first 12 years after diagnosis among patients with and without islet antibodies at diagnosis of adult-onset diabetes. Patients with two or three antibodies had severely impaired β-cell function (low to unmeasurable plasma C-peptide) after 5 years, whereas this occurred later (up to 12 years) among subjects with only ICAs or GADAs at diagnosis. Patients without islet antibodies or only IA-2As at diagnosis did not show decreases in plasma C-peptide after diagnosis during 12 years of observation. Of note, patients developing ICAs after diagnosis showed a slight but significant ($P < 0.05$) decrease in mean fasting plasma C-peptide after the occurrence of ICAs. Data are means ± SE.

instead of sulfonylurea in the early stage of treatment of LADA patients gave a sustained plasma C-peptide response, whereas most sulfonylurea-treated patients progressed to an insulin-dependent state. However, the rather similar findings in type 2 diabetic patients without islet antibodies referred to above (37) do not support a specific immunomodulating effect of insulin. Moreover, the lack of a preventive effect on autoimmune diabetes in the subcutaneous Diabetes Prevention Trial–Type 1 (40) and in oral insulin trials (41,42) does not support the idea of insulin as a specific remedy for autoimmune diabetes. Insulin improves β-cell function because of its unspecific effect on glucose toxicity.

Based on the concept that decrements in β-cell activity decrease exposure of β-cell antigens (43), diazoxide and octreotide have been used in classic type 1 diabetes but only with a slight and temporary effect (44,45). However, this approach has not yet been tested in LADA.

Heat-shock protein peptide (DiaPep277) was found to preserve endogenous insulin production in a phase II clinical trial, perhaps through induction of a shift from T-helper 1 (interferon-γ production reduced) to a T-helper 2 (interleukin-9 and -13 increased) predominance (46). Further studies are needed to clarify the putative effect of DiaPep277 on autoimmune β-cell destruction. In agreement, an anti-CD3 monoclonal antibody reduced the deterioration in endogenous insulin production and improved metabolic control during the first year of type 1 diabetes in patients with recently diagnosed type 1 diabetes (47). Anti-CD3 monoclonal antibodies may have direct effects on pathogenic T-cells. The ratio between $CD8^+$ and $CD4^+$ T-cells increased in subjects who responded with improved insulin production. Further studies are warranted to clarify the value of anti-CD3 monoclonal treatment of autoimmune diabetes. A first report of immunomodulation with subcutaneous GAD65 in LADA patients indicates that this treatment was safe, giving increased fasting p-C-peptide concentrations after 24 weeks in subjects treated with a moderate dose (20 μg) but not in subjects treated with higher doses (100 or 500 μg) or lower doses (4 μg) (48).

CONCLUSIONS

Autoimmune diabetes of slow onset is prevalent and found in 10% of phenotypic type 2 diabetic patients, actually in 25% of individuals below 35 years of age at diagnosis of diabetes. Prospective follow-up of these patients shows that complete β-cell failure occurs in almost all of these patients, but it may take up to 12 years until it develops. Although not insulin requiring at diagnosis, type 2 diabetic patients with islet antibodies have impaired β-cell function at diagnosis. Hence, insulin treatment is indicated at diagnosis. The effect of insulin in these patients is most likely against glucose toxicity and not immunomodulatory. Because of the slow progression of β-cell failure, patients with autoimmune diabetes of this type are candidates for immunomodulation. Different immunomodulatory agents have also been tried in these patients, with some effects favoring future attempts. As patients with autoimmune diabetes of slow onset develop future β-cell failure and also display disturbed β-cell function at diagnosis, we suggest that the term "latent autoimmune diabetes in adults" should be replaced. LADA is not a latent disease. We suggest autoimmune diabetes in adults with slowly progressive β-cell failure (ADASP).

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