

CLINICAL REVIEW: Type 1 Diabetes and Latent Autoimmune Diabetes in Adults: One End of the Rainbow

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Context: The aim of this review was to explore the pathogenic and clinical spectrum of type 1 diabetes, which includes a form of adult onset autoimmune diabetes usually referred to as latent autoimmune diabetes in adults (LADA). We looked at this entire range of forms of autoimmune diabetes as a spectrum of genetic and nongenetic environmental influences, diabetes-associated immune responses, and metabolic changes.

Evidence Acquisition: We assessed epidemiological, genetic, immunological, and clinical data from major articles on autoimmune diabetes, including LADA and type 1 diabetes, published since 1992.

Evidence Synthesis: Data analysis of autoimmune diabetes indi-

cates that type 1 diabetes and LADA occupy different poles of the same spectrum.

Conclusion: Evidence is presented that LADA represents one end of a rainbow encompassing type 1 diabetes. The clinical nature and management of autoimmune diabetes poses important therapeutic questions regarding conventional therapy for hyperglycemia as well as therapy aiming to protect residual β -cell function. Limiting loss of endogenous insulin secretion using immunomodulation could be valuable, not only for LADA but also for type 1 diabetes. (*J Clin Endocrinol Metab* 91: 1654–1659, 2006)

TYPE 1 DIABETES RESULTS from the destruction of the insulin-secreting islet cells by an immune mediated process. This adverse immune response is induced and promoted by the interaction of genetic and environmental factors and is one of a group of autoimmune diseases that affect about 10% of the population in the developed world. Type 1 diabetes used to be defined in terms of the absolute need for insulin therapy (insulin-dependent diabetes) or, before that, the age at onset of the disease (juvenile onset diabetes). These defining features were then abandoned in favor of the term type 1 diabetes (1) when it became apparent that not everyone with autoimmune diabetes is either a juvenile or necessarily exhibits an absolute insulin requirement.

Individuals diagnosed with autoimmune diabetes, *i.e.* diabetes associated with diabetes-associated autoantibodies, when they are adults may not initially require insulin treatment and have been classified as having latent autoimmune diabetes of adults (LADA) (2, 3), latent because without testing for diabetes-associated autoantibodies it would not be possible to identify these patients as having autoimmune diabetes and adult because at that time it was suggested that this form of diabetes was not present in juveniles. This form of diabetes has also been called slowly progressing insulin-

dependent diabetes (4) or type 1.5 diabetes (5). The aim of this article was to explore the clinical and pathogenic spectrum of autoimmune diabetes that extends into and includes LADA.

LADA is defined by three features including: adult age at diagnosis, the presence of diabetes-associated autoantibodies, and delay from diagnosis in the need for insulin therapy to manage hyperglycemia. However, the first and last are not categorical traits, being dependent on the mode of ascertainment and decision making by physicians. The second feature lacks disease specificity because it is based on positivity for autoantibodies found in type 1 diabetes mellitus. In a recent review (6), it was suggested that LADA patients should be diagnosed with non-insulin-requiring diabetes at age 30 yr or older and that age (range 30–70 yr) was also used in a major European Union initiative (www.actionlada.org); in addition, both defined LADA to include patients who had 6 months without insulin treatment after diagnosis (6). Other large studies of autoimmune non-insulin-requiring patients have included selected cases, cases not taking any pharmacological agent, or avoided a definition entirely (7–9). Difficulties with the performance of islet cell and insulin autoantibody assays precluded them from being used routinely in defining LADA. Because insulinoma-associated antigen (IA)-2 autoantibodies are usually found with glutamic acid decarboxylase (GAD) autoantibodies but rarely in LADA, this condition is broadly defined by the presence of GAD autoantibodies. However, GAD autoantibodies are also found in type 1 diabetes mellitus, so it follows that using them in the definition of LADA lacks disease specificity (10). The epidemiology of LADA is also influenced by geography,

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Abbreviations: GAD, Glutamic acid decarboxylase; HLA, human leukocyte antigen; IA, insulinoma-associated antigen; IAA, insulin autoantibody; ICA, islet cell autoantibody; LADA, latent autoimmune diabetes in adults.

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genetic susceptibility, environmental factors, gender, and age at diagnosis. In Northern Europe and North America, about 5–10% of newly diagnosed non-insulin-requiring diabetes patients have LADA, according to the mode of ascertainment, the sourced population, the age of the patient (frequency is higher in younger age groups), and the definition of the disease (5, 6, 10).

LADA at One End of a Spectrum of Genetic Susceptibility

The epidemiology of autoimmune diabetes including type 1 diabetes is influenced by genetic susceptibility, which modifies age at onset (6). There is evidence in autoimmune diabetes for a continuum of genetic susceptibility, which extends from a marked effect in childhood-onset type 1 diabetes to the relatively limited effect detected in LADA (Table 1). Survival analysis estimates that nondiabetic identical twins of probands diagnosed with type 1 diabetes under 25 yr of age have a 38% probability of developing diabetes, compared with only 6% for twins of probands diagnosed later (11–13) (Table 2). Such a remarkably low twin concordance for adult-onset type 1 diabetes implies that the genetic impact in adult-onset diabetes is limited (14, 15), favoring a substantial impact of environmental factors. There is an age-related continuum in diminishing twin concordance, suggesting that the decline in genetic influence is gradual, consistent with a phased influence on a single disease, type 1 diabetes, rather than an age-related step-wise effect resulting from two distinct diseases. There are, as yet, no twin studies of LADA. Of genes implicated in the genetic susceptibility to type 1 diabetes and LADA, the most important, for both, are in the histocompatibility [human leukocyte antigen (HLA)] region of chromosome 6 (14).

HLA alleles associated with type 1 diabetes susceptibility include HLA DR3, DQB1*0201, and DR4, DQB1*0302, whereas others are associated with disease protection, *e.g.* HLA DR2, DQB1*0602 (16–19). Children with type 1 diabetes show an increased prevalence of the heterozygous alleles HLA DR3, DQB1*0201, and DR4, DQB1*0302, the proportion of heterozygotes declining with age at diagnosis (19). Children with the diabetes-protective HLA DR2, DQB1*0602, are unlikely to develop diabetes (20), whereas in type 1 diabetes of adult-onset and LADA, the same alleles carry less protection (21, 22) (Table 1). Nevertheless, both the latter and LADA show HLA genetic susceptibility with little or no HLA genetic protection (19–21).

Strikingly, even adults with non-insulin-requiring diabetes without the diabetes-associated autoantibody to GAD

TABLE 2. Concordance for type 1 diabetes in identical twins according to age at clinical onset in the index twin

	Young-onset, % (yr)	Older-onset, % (yr)
UK/US (Ref. 11)	38 (<25)	6 (>25)
US (Ref. 12)	44 (<15)	13 (>15)
Finland (Ref. 13)	50 (<10)	23 (>10)

Note the substantially lower concordance rates in the older-onset twins consistent with a marked nongenetically determined effect causing diabetes in them.

have an excess of diabetes-associated HLA alleles and are relatively young and lean (7, 23–25). Age-related genetic factors also influence the risk of type 1 diabetes. Not only is the age incidence of type 1 diabetes lower in adults than in children, the range of incidence across European countries is also reduced in adults (26). Furthermore, there is a male excess in incidence that becomes evident during puberty and is most striking in the age group 25–29 yr (26).

A recent, albeit small, genetic study (8) found similar HLA susceptibility genes in both type 1 diabetes and LADA. Other genes have been linked to type 1 diabetes and these genes, including TNF α , TNF β , IL-10, IL-6 gene polymorphisms, and IL-18 gene promoter polymorphism, but they have yet to be studied comprehensively in LADA (27, 28). Other gene polymorphisms within the CTLA4, PTPN22, IRS-1, ICOS, and SUMO4 genes confer a substantial risk to type 1 diabetes with odds ratios between 1.8 and 2.5 but have not been studied in LADA (29).

In the light of these observations, it remains possible that LADA represents one end of a rainbow of autoimmune diabetes, which is distinguished from classic type 1 diabetes only because it is diagnosed in adulthood and presents with some clinical, anthropometric, and metabolic features more commonly associated with type 2 diabetes.

LADA in a Spectrum of Nongenetic Influences

Nongenetic factors play a major role in causing type 1 diabetes as shown by studies of populations that have migrated, populations with changing disease incidence, and twins. We know little of the current incidence of autoimmune diabetes in adults and LADA. The incidence of a range of autoimmune diseases, including diabetes, has increased notably over the last three decades (30). The current low selection density and relative stability of HLA gene polymorphisms indicates that this increasing incidence cannot be due to genetic selection pressures and is most likely the result of nongenetic factors (10, 15).

Unfortunately, population studies are of limited value in

TABLE 1. Genetic, immunological, and metabolic differences between childhood-onset and adult-onset type 1 diabetes and LADA

	Children T1DM	Adults T1DM	LADA
Age at diagnosis	Childhood	Adulthood	Adulthood
Identical twin concordance rate	Moderate (<i>e.g.</i> 38%)	Very low (<i>e.g.</i> 6%)	?
HLA-DR3/ DR4	Moderate (<i>e.g.</i> 37%)	Low (<i>e.g.</i> 13%)	Low-moderate (<i>e.g.</i> 22%)
Protective HLA genotype (HLA-DR2)	Very low (<i>e.g.</i> 9%)	Low (<i>e.g.</i> 15%)	Low-moderate (<i>e.g.</i> 22%)
Autoantibodies	IAA GAD IA-2	GAD IA-2	GAD IA-2
Plasma insulin	Very low	Low	Low

Note that the children, compared with the others, have a higher identical twin concordance rate, frequency of HLA genetic susceptibility heterozygosity and insulin autoantibodies, and lower serum insulin levels. HLA DR3/4 is found in about 6% of North American and European control populations. Data compiled from different sources (6, 11, 17, 19–22). T1DM, Type 1 diabetes mellitus; ?, rate unknown.

identifying the impact of nongenetic factors because it is difficult to segregate genetic from environmental influences. However, changes in disease incidence within a genetically stable population are important when disease incidence rises rapidly or changes abruptly as in migrants (31, 32). Migrant studies support a role for environmental factors influencing disease incidence (32, 33). Type 1 diabetes incidence in Asian children in families who have migrated to Britain increased from 3.1 per 100,000 per year in 1978–1981 to 11.7 per 100,000 per year in 1988–1990, much higher than in their native Karachi (1 per 100,000 per year) (29, 30). However, Sardinian migrants moving to continental Italy retained the high incidence of the ancestry region, suggesting that it is the genetic susceptibility that determines the prevalence of the disease in response to the environmental factors (34). There are no comparable migration studies of adults with type 1 diabetes or of LADA patients. On the other hand, the identical twin concordance for adult-onset type 1 diabetes is low, implying that the genetic impact on this form of diabetes is limited, which in turn suggests a major impact of environmental factors (10). The declining identical twin concordance rate for type 1 diabetes with increasing age appears to be a continuum and not a categorical phenomenon, in line with an age-related spectrum of environmental impact on the etiology of autoimmune diabetes. However, there are no twin studies in LADA, so it is unclear whether this spectrum extends into that form of autoimmune diabetes.

LADA at One End of a Spectrum of Diabetes-Associated Immune Responses

At birth, children of mothers with diabetes may have islet cell autoantibodies (ICAs), insulin autoantibodies (IAAs), and GAD autoantibodies. But these autoantibodies can also be found in the maternal serum and are probably placentally transferred to the child because autoantibody specificities are similar in mother and cord blood and are not usually detected in the infants of mothers without such autoantibodies (35–37). Passively acquired maternal autoantibodies disappear after birth as expected but can subsequently be replaced by the infant's own autoantibodies.

Diabetes-associated autoantibodies can appear at a later stage. In one study, three of 58 infants of diabetic mothers developed IAAs, ICAs, and GAD *de novo* by 2 yr of age, and only then were autoantibodies associated with diabetes risk (35), and in another study, 137 children with ICAs from a prospective Finnish study of 4590 consecutive newborns with the disease-risk HLA-DQB1, IAAs, and GAD autoantibodies usually appeared in childhood before ICAs, whereas IA-2 autoantibodies usually appeared later when IAAs are uncommon (38). In contrast to LADA and adult-onset type 1 diabetes, children often have IAAs at diagnosis and, in them, IAA is highly predictive of the disease (39). Because seroconversion continued up to at least age 10 yr of age, it follows that the induction event with activation of immune response to produce diabetes-associated autoantibodies is not confined to early childhood. It remains unclear whether the age at clinical diagnosis is in part dependent on the age at which an environmental event activates the immune response. If this is the case, then the immune process that leads

to adult-onset type 1 diabetes and LADA would be induced later in them than in childhood-onset type 1 diabetes.

Taken together these observations suggest that activation of the diabetes-associated immune process can occur in early childhood when it is more likely to be associated with IAAs in those who progress to childhood-onset type 1 diabetes. But the induction of diabetes-associated autoantibodies is not confined to early childhood. Currently we have no clear evidence identifying the age of induction of diabetes-associated autoantibodies in those subjects who develop either adult-onset type 1 diabetes or LADA. However, we know that these diabetes-associated autoantibodies, when detected in adult life, are predictive of an ongoing β -cell destructive process.

In this respect the prevalence of autoantibodies to protein tyrosine phosphatase isoforms IA-2 and IA-2 β /phogrin has been recently examined in a cohort of adult U.K. Prospective Diabetes Study patients thought to have type 2 diabetes to determine whether these autoantibodies predict a requirement for insulin therapy (37). In this cohort the presence of IA-2A was infrequent (about 2%), associated with the HLA-DR4 haplotype as is the case in classic type 1 diabetes and highly predictive of insulin therapy (positive predictive value 60%). The measurement of IA-2 β A does not provide additional information (40).

LADA at One End of a Spectrum of Metabolic Changes

There is evidence in autoimmune diabetes for a continuum of metabolic changes, predominantly decreased insulin secretory capacity, but also insensitivity to insulin. These extend from the severe changes seen in childhood-onset type 1 diabetes to the relatively minor changes initially detected in LADA.

Some individuals pass through a prediabetic stage of impaired glucose tolerance or even non-insulin-requiring diabetes before becoming frankly insulin dependent (41). Diabetes Prevention Trial of Type 1 Diabetes detected 585 relatives of type 1 diabetic patients who had ICAs plus either IAAs or low first-phase insulin response to iv glucose (42). Of these, 427 had normal glucose tolerance, 87 impaired glucose tolerance, and 61 were diabetic, yet asymptomatic (39). Of the latter, those with impaired fasting glucose were significantly older (mean age 21 yr) than those with normal fasting glucose (mean age 12 yr). These subjects with asymptomatic autoimmune diabetes resemble LADA, but their age is less than 30 yr precluding the diagnosis. It follows that some patients with autoimmune diabetes pass through a phase of altered glucose levels including non-insulin-requiring diabetes before becoming insulin dependent, and the frequency of this phase, to a degree, is age dependent. It remains to be determined whether all children with diabetes-associated autoantibodies will progress to diabetes, let alone insulin-dependent diabetes. The rate of progression to clinical diabetes is more rapid in patients presenting younger than 5 yr of age than in those presenting much later (43). Histological evidence supports this contention: islet β -cells tend to be absent within 12 months of diagnosis in patients aged younger than 7 yr but detected for longer periods in

older patients (44). Variability in progression to clinical diabetes can even be detected in very young children; for example, of children identified between 1 and 5 yr of age with diabetes-associated autoantibodies and subnormal insulin responses, half of them progress rapidly to diabetes, whereas the remainder are free from diabetes up to 4 yr later (45). Other studies have noted such variable progression to type 1 diabetes, which is more rapid in obese than lean children (46) and in children than adults (47–50). From these observations it follows that there is a spectrum in the rate of metabolic decompensation during the prediabetic period in autoimmune type 1 diabetes, but no data are available, as yet, in LADA.

Insulin secretory capacity is less in children than adults at the onset of type 1 diabetes and after diagnosis deteriorates more rapidly. A study of 235 consecutive cases with newly diagnosed type 1 diabetes found that those aged younger than 7 yr had the lowest baseline residual insulin secretion and required the highest insulin dose for optimal control, whereas the older the age at diagnosis, the higher was the basal C-peptide level (51). Patients with LADA also have reduced fasting and stimulated C-peptide at diagnosis, although the levels of C-peptide are higher than those found in children and similar to those found in adult-onset type 1 diabetes (8). However, after diagnosis, the C-peptide levels have been reported to fall more rapidly in childhood-onset type 1 diabetes than in adult-onset type 1 diabetes and in the latter more rapidly than in LADA (52–55). Furthermore, persistent C-peptide secretion, implying less aggressive disease, is detected in more adults than adolescents after diagnosis of type 1 diabetes and in more adolescents than prepubertal children with diabetes (52–54). Other studies report a quite rapid loss of C-peptide even in LADA, which argues against a chronic destructive process in that condition (6, 55, 56). In summary, there is a continuous spectrum of loss of insulin secretory capacity, the severity of which can be age related, being more severe in children than adults with type 1 diabetes and more severe in the latter than in LADA subjects, although some patients with LADA may show a rapid loss of insulin secretory capacity.

The metabolic decompensation that leads to frank diabetes could result from either increased linear growth, which has been linked to diabetes risk, or increased childhood obesity, which has been correlated with age at presentation (10, 46). People with LADA may well have more severe loss of insulin sensitivity than in childhood-onset type 1 diabetes, but there are only two small studies (57, 58) considering insulin sensitivity in LADA, and both used the homeostasis model of assessment, whereas no studies have used the gold standard euglycemic hyperinsulinemic clamp. Certainly in LADA the frequency of the metabolic syndrome, usually associated with insulin resistance, although less prevalent than in type 2 diabetic patients of similar age, is more prevalent than in the general population (9). In a recent report, the metabolic syndrome, which is found in approximately 22% of the North American population was identified in 74% of those with LADA but in significantly more subjects with type 2 diabetes (84%) (9).

It is likely, therefore, that within autoimmune diabetes, including both type 1 diabetes and LADA, there is an age-

related spectrum of decreasing insulin secretory capacity and increasing insulin insensitivity associated with the metabolic syndrome. The distinction between LADA and adult-onset classical type 1 diabetes is a matter of debate. It is possible that the distinction between the two is one of degree, with the classical type 1 diabetes being at one end of the spectrum and LADA, when it remains insulin independent, being at the other end.

A Spectrum of Clinical Management in LADA

Type 1 diabetes progresses to insulin dependence usually within 2 yr of the clinical diagnosis as noted in the preinsulin era. Before 2 yr some patients may have a partial or complete remission when insulin therapy is not required (59). Of LADA patients, in one study (7), 94% required insulin treatment by 6 yr as compared with only 14% in those initially non-insulin-requiring diabetes patients without either GAD autoantibodies or ICAs. Progression to insulin dependence in LADA patients was more rapid in those aged younger than 45 yr than in older cases (7). It follows that patients with autoimmune diabetes, including both type 1 diabetes and LADA, are at high risk of progression to insulin dependence, but that risk declines with age at diagnosis.

It is well established that insulin is the treatment of choice for type 1 diabetes, but there is no established management strategy for patients diagnosed with LADA (60–65). The European Union, therefore, funded a major initiative (ACTION-LADA) to study the characteristics of LADA and report on how to treat it. In considering how to treat LADA, some important questions arise as to our broad management of autoimmune diabetes. Because the predominant defect in autoimmune diabetes is loss of insulin secretion, should we treat the disease with insulin irrespective of the level of dependency on insulin? Autoantibody positive, initially non-insulin-requiring, diabetic patients initially treated with sulfonylureas have been found to require insulin earlier than autoantibody-negative patients, but sulfonylureas did not have an impact on the need for insulin treatment or the time to progression to insulin therapy (41).

Metformin is routinely offered to patients with non-insulin-requiring diabetes, but its specific role in LADA is unclear, and the drug may be contraindicated in those with LADA because there is a theoretical risk of severe metabolic disturbance in individuals who progress to insulin dependency while on it. Intriguingly, however, there is limited evidence that metformin could be of value, even in patients with type 1 diabetes. For example, in one study, adolescent type 1 insulin-dependent diabetes patients given metformin subsequently showed a significantly lower hemoglobin A1c and reduced insulin requirements, compared with those not taking metformin (62).

Thiazolidinediones also might theoretically be of value because they not only improve insulin sensitivity but also have an antiinflammatory effect and protect nonobese diabetic mice, a well-established model of autoimmune diabetes, from developing diabetes (63). In a small study of LADA patients in China (64), there was a significant improvement in C-peptide but not hemoglobin A1c in patients receiving rosiglitazone plus insulin, compared with insulin alone.

Because the primary defect in autoimmune diabetes is loss of insulin secretion, treatment should aim to restore islet insulin secretion. Therapy to prevent progression toward insulin dependency could include insulin or immunomodulation, given the inflammatory nature of the disease process thought to cause insulin secretory cell destruction. The optimal insulin regimen is unclear; given the broad loss of insulin secretory capacity, it might be argued that the early introduction of a long-acting insulin could be beneficial. Alternatively, the loss of rapid insulin release in LADA patients suggests that replacement with a fast-acting insulin would be more valuable.

One study in Japan of patients with LADA compared early treatment with insulin given as multiple injections with sulfonylureas (61). Although of limited power, this study did show a statistically significant persistence of C-peptide in the insulin-treated group as compared with the sulfonylurea group with the proviso that the insulin-treated group had preserved insulin secretory capacity and a high titer of GAD autoantibodies at the start of the study (61). An alternative interpretation of this study is that sulfonylureas are disadvantageous, in support of which sulfonylureas could theoretically promote apoptosis, apoptosis being one mechanism whereby insulin-secreting cells could be destroyed in autoimmune diabetes.

A pilot phase 2 trial in LADA patients (65) found that a tolerance induction plan using alum-formulated whole GAD (Diamyd) had a significant effect on the C-peptide response to a mixed meal consistent with modulation of the aggressive process. Another phase 2 trial in LADA patients using the peptide analog of heat shock protein 60 (Diapep 277) has been completed after initial positive results in protecting residual β -cell function in adult-onset type 1 diabetes patients (66) and in experimental models of the disease (67). These immunomodulatory studies, although small and preliminary, pioneer a novel approach toward the maintenance of islet cell function, itself a new field in the management of autoimmune diabetes.

In conclusion, LADA, whether viewed genetically, immunologically, metabolically, or clinically, occupies one end of a rainbow of features associated with autoimmune diabetes. The management and prevention of LADA need to be investigated to define the best strategy for treating this most prevalent form of autoimmune diabetes.

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