Review Article

Latent autoimmune diabetes of adults: From oral hypoglycemic agents to early insulin

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ABSTRACT

Approximately 10% of phenotypic type 2 diabetics have islet autoantibodies and are referred to as having latent autoimmune diabetes of adults (LADA), and they land on early sulfonylurea failure and require insulin. Diagnosing LADA has treatment implications because of high risk of progression to insulin dependency. But often there is delay in insulin therapy, as there are no recommendations for islet antibody testing in adult-onset diabetes currently. LADA clinical risk score can identify adults at high risk who may benefit from antibody testing. The optimal treatment of LADA is not established. Early insulin therapy helps to achieve good metabolic control and better long-term outcomes by preserving β-cells and endogenous C-peptide secretion. Sulfonylureas are better avoided as they exhaust β-cells; glitazones and exenatide have favorable outcomes, whereas metformin needs to be used with caution. Understanding LADA will also bring new windows in managing type 1 diabetes. Information acquisition was done by reviewing the medical literature published since 1987, with particular attention to the natural history, genetic factors, and treatment of LADA.

Key words: Autoimmune, insulin, islet autoantibodies, latent autoimmune diabetes of adults, sulfonylurea failure

Introduction

Latent autoimmune diabetes of adults (LADA), also known as type 1.5 diabetes,[1] is adult onset autoimmune diabetes which shares features of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). The onset of LADA is in adult life (usually age >30 years), and the disease is at least initially not insulin-requiring, so the patients appear clinically to be affected by T2DM. But these patients have islet autoantibodies, most commonly glutamic acid decarboxylase (GAD) antibody, relatively low C-peptide secretion, and a higher rate of progression to insulin dependency, behaving like T1DM patients.[2] Clinical dilemma exists in initial diagnosis, but early diagnosis and interventions can influence the speed of progression toward insulin dependency.

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Position of Latent Autoimmune Diabetes of Adults in Diabetes Spectrum

At one end of the spectrum, there is T1DM with chronic inflammation of the islet as the pathogenesis. At the other end of the spectrum, T2DM is associated with systemic inflammation. And somewhere between these extremes, LADA shares features of both, thereby raising the question of its pathogenesis. The role of obesity and the degree of insulin resistance in LADA are other areas of controversy. Insulin resistance in LADA has been reported to be less than in T2DM and comparable to T1DM.[3,4] If we exclude glucose as a variable, metabolic syndrome is not more prevalent in autoimmune diabetes than in control subjects.[5] T1DM has strong human leukocyte antigen (HLA) genetic predisposition, T2DM has no HLA association, and LADA has less marked HLA link than T1DM, which could be the reason for late onset.[6] The pathological hallmark of T1DM, insulitis, is also present in LADA, but less pronounced, which protects β-cells from extensive T-cell destruction, at least initially.[7] Islet cell inflammation suggested by islet autoantibodies and elevated C-reactive protein (CRP) levels may provide a marker for progression to T1DM.[8] Systemic inflammation with acute-

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phase response (i.e., elevated CRP) plays a fundamental role in the pathology of T2DM. Other markers of systemic inflammation, tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1, and plasminogen activator inhibitor (PAI)-1, are also elevated in these people.[9] Regarding islet cell autoimmunity in LADA, Shimada *et al.* have reported their findings of a 65-year-old woman originally diagnosed as T2DM with residual β-cell function. They found signs of insulitis, predominantly characterized by CD4+ T cells; however, elevated CRP was not reported, indicating that markers of systemic inflammation are not linked with LADA.[7] In LADA patients, initial C-peptide levels are higher than in classic T1DM subjects, which may be the reason for initial non–insulin-dependent state. Progression to insulin dependency over a period of a few years results from substantial loss of C-peptide secretion, approaching levels seen in T1DM. Whatever be the pathogenesis, the age at diagnosis influences the amount of β-cell mass left, which is more in patients with LADA as opposed to the young T1DM subjects.[10] In T2DM, the C-peptide levels are normal or even raised at the time of diagnosis [Table 1].

Approach to a Patient Suspected with Latent Autoimmune Diabetes of Adults

T1DM patients require insulin from the very beginning, whereas T2DM patients may require insulin in the long run when they reach the stage of relative insulin deficiency. For many years, insulin dependency was thought to specifically characterize T1DM, but the clinical criterion of early insulin dependency, and the pathogenetic criterion of islet cell autoantibodies (ICAs) leading to β-cell damage do not match in a number of cases. An etiologic classification criterion was therefore chosen to subgroup this different type of diabetes.[11] The term "latent autoimmune diabetes of adults" was introduced to define adult diabetic patients initially not requiring insulin, are clinically difficult to distinguish from T2DM subjects and test positive for immune markers of T1DM, and a number of such cases progress to early insulin dependency.[12] In the UK Prospective Diabetes Study (UKPDS), 12% of patients with type 2 diabetes were found to have ICA or glutamic acid decarboxylase antibody (GADA) at diagnosis and 4% had both. The phenotype of patients with both antibodies was similar to that of classic type 1 diabetes and, at different ages, 59–94% required insulin within 6 years, compared with 5–14% in those with neither ICA nor GADA.[13] Most adults with non-insulin requiring, autoimmune diabetes at diagnosis become insulin-requiring within 3–6 years.[14,15] Since these patients are initially treated with oral hypoglycemic agents (OHA), early OHA failure gives clue to clinical suspicion. Clinical feature that is significantly more frequent in LADA is designated as a distinguishing clinical feature and a "*LADA clinical risk score*," based on the total number of distinguishing features, is calculated. In a retrospective study, five clinical features were more frequent in LADA compared with T2DM at diagnosis:[2]

1. Age of onset < 50 years
2. Acute symptoms (polydipsia / polyuria /unintentional weight loss)
3. Body mass index (BMI) < 25 kg/m^2
4. Personal history of autoimmune disease (HLA DR3/DR4-related)
5. Family history of autoimmune disease (HLA DR3/DR4-related)

In a prospective study, the presence of at least two of these distinguishing clinical features (LADA clinical risk score ≥ 2) had a 90% sensitivity and 71% specificity for identifying LADA, and a negative predictive value for a LADA clinical risk score ≤1 of 99%.[2]

Age, BMI and autoimmune diseases are highly variable in population; and acute symptoms of hyperglycemia can occur in any form of diabetes. The clinical risk score cannot by itself predict autoantibodies, but highly indicates for antibody testing and helps early diagnosis.

Diagnosis

LADA was first identified in a subset of phenotypic T2DM individuals with positive ICAs.[14] In an attempt to standardize the definition of LADA, the Immunology of Diabetes Society has recently proposed the following criteria: patients should be at least 30 years of age, positive for at least one of the four antibodies commonly found in type 1 diabetic patients (ICAs, autoantibodies to GAD65, IA-2, or insulin), and not treated with insulin within the

Table 1: Comparison of markers in type 1 diabetes mellitus, latent autoimmune diabetes of adults, and type 2 diabetes mellitus

Genetic/other markers	T1DM	LADA	T2DM
Islet cell antibodies	Positive, may test positive before onset	Positive, helps differentiation from T2DM	Negative
Insulin autoantibody	Often detected	Often detected	Negative
Islet antigen 2	Often positive in newly diagnosed T1DM	Often detected	Negative
Glutamic acid decarboxylase antibody	Common in adults than in children	More common than in T1DM	Rare, positive may indicate LADA
HLA link	High	Low	Negative
Insulin/C-peptides	Very low	Low	Normal to high

T1DM: Type 1 diabetes mellitus, LADA: Latent autoimmune diabetes of adults, T2DM: Type 2 diabetes mellitus

first 6 months after diagnosis.[4] In an attempt to standardize the diagnosis, three criteria are currently recommended, but all of them have some pitfalls.[16] The clinical criteria 1 and 2 are highly dependent on physician's decisions, and criterion 3 is not specific for LADA.[17]

Criterion 1: Adult age at onset: Various cut-off ages values have been used (between 25 and 45 years), but now the most widely accepted lower limit is 30 years of age.[14,16,18] However, since adulthood starts earlier in life, this limit might not be all inclusive.

Criterion 2: Lack of insulin requirement for at least 6 months after diagnosis: Time of insulin requirement is used to distinguish LADA from T1DM, but there is always bias in the initiation of insulin treatment, as it does not solely depend on disease process, but rather on physician's clinical judgment.[19] The nature of the disease, symptoms and level of hyperglycemia at diagnosis also influence the period of insulin independency.[17]

Criterion 3: Presence of autoantibodies (at least one): ICAs, autoantibodies to insulin (IAA) and tyrosine phosphatase-like insulinoma-associated protein 2 (IA-2) have been reported to be rather infrequent, so the diagnosis of LADA relies on identifying GADA, which is the best single marker for screening. Epitope specificity, antibody levels, and concomitant presence of ICAs subcategorize LADA with a different risk toward insulin dependency.[20] In a study, GADA was found to be significantly higher in the insulin-deficient group (76%) than in the non–insulin-deficient group (12%), and this difference was substantially greater than that shown for ICAs[12] [Table 2].

The latest Diabetes Antibody Standardization Program (DASP 2009) demonstrated 76% sensitivity and 95.7% specificity for anti-GAD and 64% sensitivity and 98.9% specificity for anti-IA2, and standardization is still ongoing.[21] No acceptable therapy has been demonstrated yet to prolong the survival of islet cells once diabetes has been diagnosed or to prevent the clinical onset of diabetes in autoantibody-positive subjects. Therefore, islet autoantibodies are currently not recommended in diagnosis or routine management of adult patients with diabetes. Although autoantibody-positive diabetic patients progress to absolute insulin deficiency faster, many antibody-negative patients also progress to insulin dependency with time. The clinical benefits from institution of insulin therapy to these patients are based on careful monitoring and treatment of hyperglycemia rather than diagnosis of antibodies itself. However, health guidelines may differ from individual case management. An adult patient with T2DM who has single antibody is probably at no greater risk of early insulin requirement than the one of the same age without antibodies. However, a young person with multiple autoantibodies is almost certain to need insulin soon. These factors need to be taken into consideration in counseling patients, and antibody testing will benefit in such cases.[13,22]

Table 2: Assays for islet autoantibodies

Antibody	Assay methods	Comments
Glutamic acid decarboxylase antibody	Radioimmunoassay (RIA), enzyme-linked immunosorbent assay	Generally RIA methods are used for these antibodies, but inconvenience of dealing with radioisotope has made ELISA developed for clinical utilization
Insulin autoantibodies Islet antigen 2 Islet cell antibodies	Enzyme-linked immunosorbent assay	Because ICA assays are difficult to standardize, their use has declined substantially

C-peptide: The most appropriate guide of endogenous insulin secretion and β-cell function is measurement of C-peptide because of its equimolar secretion with insulin, negligible hepatic extraction, and constant peripheral clearance at different plasma concentrations. Low C-peptide levels means loss of β-cell mass and decreased endogenous insulin secretion indicating the need for insulin initiation.[23]

Management Strategy

Eliminating symptoms of hyperglycemia, reducing long-term complications, and helping patient to achieve normal lifestyle should remain the goals of treatment in any form of diabetes. Lifestyle modification, medical nutrition therapy, screening and treatment of hypertension, hyperlipidemia, nephropathy, retinopathy, and every overall aspect of comprehensive diabetes care should be followed. Investigations should also include antibody testing for diagnosis and C-peptide levels for β-cell status. Currently, many physicians test for islet autoantibodies only if they suspect LADA. Overweight adults are presumed to have T2DM and are not tested, whereas normal-weight adults are considered to potentially have LADA and may be tested.[2] Therapeutic approach for LADA should aim not only at obtaining good metabolic control, but also allowing better preservation of the residual β-cells and endogenous insulin, since it has been proven in some studies to be associated with improved metabolic control and better long-term outcome[24,25] Studies have shown that recovery of β-cell function may occur even after the clinical onset of T1DM, involving cytokine-dependent regulatory pathways.[26] Genetic risk for autoimmune

diabetes overlaps with autoimmune thyroiditis, celiac disease, and Addison's disease. Disease risk is associated with organ-specific autoantibodies, which can be used to screen the subjects.[27] Unfortunately, there is no established therapeutic intervention for LADA, despite the fact that the affected population represents a sizeable number of patients with diabetes.

Oral hypoglycemic agents – Sulfonylureas

Sulfonylurea failure is the most common clinical setting for diagnosing LADA, so these drugs are given special consideration. These agents stimulate insulin secretion by interacting with ATP-sensitive potassium channels in β-cells, and are very effective in treating T2DM of recent onset. Despite their initial efficacy, there is progressive deterioration in β-cells and glycemic control over time. The cause might be exhaustion or desensitization of β-cells by prolonged exposure to sulfonylurea and possibly accelerated oxidative stress and apoptosis.[16] A long-term randomized control trial (RCT) compared conventional treatment (primarily with diet) to sulfonylureas and to insulin, and sulfonylureas with insulin. A total of 60% of the autoantibody-positive patients treated with sulfonylureas progressed to insulin requirement within 2 years compared with 15% of the autoantibody-negative patients.[28] It has also been suggested that stimulation of insulin release increases autoantigen expression, which could be deleterious in LADA as it might accentuate the autoimmune process. These results suggest that therapy with sulfonylureas in LADA would actually expedite the progression toward β-cell depletion and the necessity of early insulin initiation.[16,29,30]

Insulin sensitizers, metformin and thiazolidinediones

Metformin is the initial choice of drug in patients with T2DM. It acts by decreasing the hepatic glucose output and sensitizing peripheral tissues to the action of insulin. Unlike sulfonylureas, it does not cause β-cell exhaustion. Since LADA patients have some degree of insulin resistance, metformin is beneficial. But there is a potential risk of lactic acidosis in patients who progress toward insulin dependency.[16,29] The thiazolidinediones (TZDs) are good insulin sensitizers. They decrease insulin resistance and enhance glucose uptake by upregulating GLUT4 channels via peroxisome proliferator activated receptor-γ. Apart from their effect on glucose homeostasis and lipid metabolism, they decrease insulin demand and β-cell exhaustion, have anti-inflammatory effects, protecting cells from oxidative stress and apoptosis, and even facilitate β-cell proliferation.[16,31] Studies comparing rosiglitazone plus insulin with insulin alone in LADA patients showed that even though rosiglitazone plus insulin did not improve metabolic control significantly more than insulin alone, it appeared to have a beneficial effect in terms of maintaining C-peptide levels in the long term.[10,32] This group of drug seems to be appealing, but recent concerns are the harmful effects of rosiglitazone on heart; pioglitazone may be safer.

Insulin

It seems somehow paradoxical to initiate early insulin treatment in LADA, since this disease is characterized by lack of insulin requirement at onset. The rationale for early insulin therapy though would be to improve glycemic control while protecting β-cells. The exact mechanisms for the apparent beneficial effects of insulin treatment are yet to be fully understood, but it is thought that administration of exogenous insulin would allow β-cells to rest and decrease insulitis at least by decreasing their metabolism and by relieving hyperglycemic stress.[16,33] It is also suggested that active β-cells, producing high amounts of insulin, are more susceptible to immune destruction, and therefore rest to β-cells could preserve them longer. Also, as insulin itself is an autoantigen, immunization with exogenous insulin is thought to initiate an immune modulation possibly by tolerance induction or "bystander" suppression of autoreactive T-cells through release of regulatory cytokines. Subgroup analysis suggested that patients with high anti-GAD titers and preserved C-peptide response at baseline were less likely to progress to the insulin dependency, with early initiation of insulin. The optimal insulin regimen is not clear. If rapid loss of insulin release occurs early in LADA, replacement with multiple doses of insulin might be beneficial. However, from a practical point of view, it is difficult to initiate multiple insulin injection therapy very early in LADA patients, especially if their blood glucose levels are not severely elevated. In such patients, long-acting insulin can be the initial choice.[16,34,35] Recently, a 3-year follow-up study has shown that early insulin treatment in LADA not only preserves the level of metabolic control, but is also safe and well tolerated.[36]

Immune modulation

Since LADA is an autoimmune disease caused by failure to maintain tolerance to autoantigens, immune modulation may provide effective means of controlling the process by inducing tolerance. Studies are ongoing. Peptide of HSP60 (DiaPep277) has shown to protect residual β-cell function in adult-onset T1DM patients.[37] GAD65 (Diamyd), an alum-formulated whole GAD, had shown a significant effect on the C-peptide response.[38] Anti-CD3 monoclonal antibodies (anti-CD3) have demonstrated preservation of β-cell function with maintenance of higher endogenous insulin secretion and concomitant reduction in A1C levels and insulin usage in T1DM subjects. These agents could be possible beneficial interventions also for LADA patients.[39,40]

Incretin drugs like Exenatide, Liraglutide (Glucagon-like peptide-1 agonists) and Sitagliptin (Dipeptidyl peptidase-IV inhibitor) that amplify glucose-stimulated insulin secretion and that are thought to promote islet growth might be helpful in managing individual patients. Studies are yet to prove their benefits in LADA patients.

Conclusion

LADA prevalence of about 10% along with T1DM almost doubles the population of early insulin-requiring patients. Since progression of LADA is slower than T1DM, windows of opportunities for treatment are better. But there are no standard guidelines currently as its pathogenesis and natural history is yet to be fully understood. Till clarity comes out, what can we do? Since our main target in management of LADA is the possible preservation of β-cells to prolong insulin independency, we should be able to predict the at-risk group for early intervention. Prediction cannot prevent but can at least modify the disease process for better outcomes. We can categorize the suspects into two groups: those with lower risk for LADA (LADA clinical risk score ≤ 1) and those with higher risk for LADA (LADA clinical risk score ≥ 2). GADA having high specificity should then guide the diagnosis. Sulfonylureas should not be used as first-line therapy, and not at all if possible since they further exhaust β-cells. Metformin may be used, especially in obese subjects with insulin resistance, but the possibility of lactic acidosis with insulin dependency should always be kept in mind. Agents like TZDs and exenatide, which also have potential beneficial effects on preservation/augmentation of β-cell mass, might be a good therapeutic option, but TZDs alone may not achieve good glycemic control. Insulin therefore seems the cornerstone of management. Based on C-peptide levels, insulin should be initiated as early as needed, and as early as possible. Patients are always reluctant to start insulin, especially if they have to switch from OHA very early, so educating and counseling the patients is very important. Immunomodulatory agents might be of benefit, but clinical studies are yet to clearly demonstrate their benefit in LADA. More studies are needed to come to a definite conclusion, which, if successful, may also help in preventing insulin dependency in younger individuals who are susceptible to type 1 diabetes.

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