Latent Autoimmune Diabetes in Adults (LADA): AKA Slow Diabetes and Diabetes 1.5
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Purpose

The purpose of this course is to familiarize the health practitioner with latent autoimmune diabetes (LADA) (AKA slow diabetes, diabetes 1.5) and to help to differentiate LADA from diabetes mellitus type 1 and diabetes mellitus type 2.

Goals

Upon completion of this course, the health practitioner should be able to:
- Briefly describe the history of diabetes.
- Explain the use of the terms LADA, slow diabetes, and diabetes 1.5.
- Explain the pathophysiology of LADA.
- List and explain at least 6 differences between LADA and diabetes mellitus type 2.
- Explain the three primary criteria for diagnosing LADA.
- Discuss 4 autoantibody tests.
- Discuss treatment options and implications for use of 5 classes of diabetes mellitus 2, drugs.
- Discuss complications related to LADA.

Introduction

Diabetes was identified by the Greeks 2000 years ago, but insulin—an effective treatment—was first developed in 1921. In 1935, two forms of diabetes mellitus—type 1 and type 2—were differentiated although oral medications to treat type 2 diabetes weren't created until the 1950s. Since then, researchers have continued to clarify the differences between the two forms of diabetes and have recognized pre-diabetic risk factors. Diabetes mellitus type 1 (formerly juvenile-

onset diabetes), is characterized by destruction of beta cells in the pancreas. As cells are destroyed, insulin production falls and then ceases. Diabetes mellitus type 2 (affecting 90% of those with diabetes) is characterized by insulin resistance and sometimes impaired (although not absent) insulin production. With type 2, the tissue cells are unable to effectively uptake glucose. **[See CE course: Diabetes Mellitus: Type 1, Pre-diabetes, and Type 2]**. However, it has become clear that simply dividing diabetes into two types is less than accurate. Research in the 1970s indicated that there was yet another type of diabetes. This form of diabetes is called by various names: slow diabetes, latent autoimmune diabetes in adults (LADA), and diabetes 1.5.

What is LADA?

The term "latent autoimmune diabetes in adults" (LADA) is used more commonly than "slow diabetes" or "diabetes 1.5" and is probably a more accurate description. Diabetes type 1 was previously called juvenile-onset diabetes because onset was usually before age 30 and often in childhood. Type 1 is the most common type in children under 12. "Juvenile-onset" was changed to "type 1" to recognize the growing number of people diagnosed with adult-onset insulin-dependent diabetes. LADA is generally classified as a sub-type of diabetes mellitus type 1 although recent research suggests that is not exactly correct because LADA has some characteristics of diabetes mellitus type 2 (thus "diabetes 1.5"). The onset of LADA is slower than diabetes mellitus type 1 (thus "slow diabetes").

LADA is clearly not the same as diabetes mellitus type 2, which is characterized by insulin resistance and occurs primarily in older adults although there has been an increase in children diagnosed with type 2, probably because of increased rates of obesity. Much research has shown that those with LADA have less insulin resistance than those with diabetes mellitus type 2, but other research has shown that insulin resistance is similar. However, this may vary by population and geography.

With autoimmune diabetes (type 1 or LADA), beta cells that secrete insulin are destroyed. Researchers believe that autoantibodies trigger a response by T-cells, which in turn attack and destroy the beta cells. Researchers have found that the rate of beta-cell destruction varies with the age of diagnosis. Beta-cell function declines rapidly in very young patients but slows in adolescence and slows even more in adults. Those with diabetes mellitus type 1 are usually insulin dependent within 6 months of diagnosis. With LADA, it appears that some

protective immune response slows destruction of beta cells in comparison with the rapid destruction found with typical diabetes mellitus type 1. Thus, the older a patient is at the onset of symptoms, the longer it will probably take for the pancreas to stop producing insulin altogether.
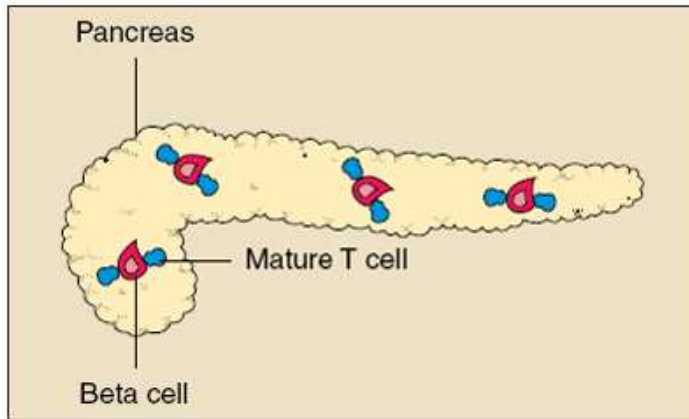
J Kelly, NIAID

As more and more cells are destroyed, insulin production falls. Patients with LADA do not require insulin at diagnosis but usually need insulin within a few years. While patients also often have some degree of insulin resistance, the primary problem relates to insulin production.

How do LADA and diabetes mellitus, type 2, differ?

Too often patients are simply diagnosed with diabetes mellitus type 2 on the basis of age rather than clinical findings or etiology. Patients with LADA tend to have a lower body mass index (BMI), and this is one aspect of differentiation, but it doesn't hold true for all adults because those diagnosed at an older age may have some weight gain consistent with aging. However, the body distribution of fat may differ. Metabolic syndrome (central obesity, hypertension, low HDL, high triglycerides) is common with diabetes mellitus type 2 but not with LADA. While individuals may vary widely in presentation, there are some general characteristics that can help to differentiate LADA from diabetes mellitus type 2.

Characteristic	LADA	DM, type 2
Insulin resistance	No, or mild to moderate.	Yes
Usual age of onset	30-50	>50
Family history of DM, type 2	No	Yes
Time from onset of	2-4 years	8-10 years

symptoms to insulin dependence		
Central obesity	No	Yes
Metabolic syndrome	No	Yes

The primary characteristics of LADA include reduced insulin production because of destruction of beta cells in the pancreas and positive autoantibodies (especially GADA). Because the pancreas is still producing some insulin when other symptoms appear, LADA is often misdiagnosed as diabetes mellitus type 2. Researchers estimate that 15 to 20% of those diagnosed with diabetes mellitus type 2 actually have LADA. This group then comprises 5 to 10% of the total number of people with diabetes, about the same percentage as those with diabetes mellitus type 1.

How is LADA diagnosed?

While there is not yet consensus over the name for LADA and whether or not it is distinct from diabetes mellitus type 1, there appears to be some consensus to what is required for a diagnosis of LADA. It's clear from these criteria that LADA falls somewhere between the continuum of diabetes mellitus type 1 and type 2:

- Autoantibodies in the blood. (Usually present in type 1 but not type 2.)
- Adult onset. (Common with type 2.)
- No need for insulin for ≥6 months after onset of symptoms. (Usually needed ≤ 6 months after diagnosis with type 1.)

Autoantibody tests are commonly used to differentiate between type 1 and type 2 diabetes. ICA, GADA, IA-2A are all associated with destruction of beta cells in the pancreas and suggest that an autoimmune process is taking place. Both the presence of GADA and ICA antibodies are predictive of insulin dependency, but GADA is most predictive.

Autoantibody tests for type 1 diabetes	
Islet cell cytoplasmic autoantibodies (ICA)	Positive in 70 to 80% of those newly diagnosed with type 1
Glutamic acid decarboxylase	Positive in 70 to 80% of those newly diagnosed with type 1.

autoantibodies (GADA)	
Insulinoma-associated-2 autoantibodies (IA-2A)	Positive in 60% of those newly diagnosed with type 1.
Insulin autoantibodies (IAA)	Positive in 50% of children with type 1 but not usually found in adults. (Not valid for someone already taking insulin as it does not differentiate between endogenous and exogenous insulin.)

Increased risk of diabetes mellitus type 2 has been associated with variants in transcription factor 7 like-2 (TCF7L2) gene on chromosome 10. Common variants are TT and CC. TT genotype is associated with decreased secretion of insulin and not insulin resistance, and those with the TT genotype are more likely to show a progression from impaired glucose tolerance to diabetes. However, the autoimmune pattern of adults >40 is different from those <40. Researchers concluded that the common variants in TCFL72 gene may differentiate young but not middle-aged GADA-positive and GADA-negative diabetic patients. Their findings suggested that young GADA-negative patients with variants in TCF7L2 have type 2 diabetes rather than type 1 and that middle-aged GADA-positive patients are different from their young GADA-positive counterparts in that they have characteristics of diabetes mellitus type 1 but also share genetic features with type 2 diabetes.

Studies show that 80% of those diagnosed with diabetes mellitus type 2 but with a positive GADA progress to insulin dependency within 6 years. If they are positive for both GADA and IA-2A, insulin dependence occurs sooner. A number of other genetic tests have confirmed that LADA appears to be an admixture of type 1 and type 2 diabetes.

Human leukocyte antigen (HLA) type is inherited, and some types of HLA are associated with autoimmune diseases. The presence of HLA-DQB1*0302 is predictive of insulin dependency. Another test that can help to differentiate LADA from diabetes mellitus, type 2 is the C-peptide test. A low C-peptide finding is consistent with decline in insulin production. A person with diabetes mellitus type 2 is more likely to have normal or high levels of C-peptide because insulin is produced, but not used adequately.

Much research is ongoing, and a definitive strategy for diagnosing and dealing with LADA has not yet been articulated because there have been inconsistencies in studies aimed at different populations and in different parts of the world. In fact, there may be multiple variations in LADA rather than one consistent profile. However, researchers suggest that the first step in differentiating LADA from diabetes mellitus type 2 is to measure GADA. If this is positive, then further testing, such as C-peptide levels and HLA typing may be indicated to better understand the patient's disease and to plan treatment. Patients with LADA are less likely to test positive for IA-2A or IAA than those with diabetes mellitus, type 1.

How is LADA treated?

The basic therapy of diet, weight loss (if necessary), and exercise is the cornerstone for both LADA and diabetes mellitus type 2. Because LADA is frequently misdiagnosed as diabetes mellitus type 2, the approach to treatment is often the same. One problem is that initial treatments for diabetes mellitus type 2 may work well, leading the physician to believe the diagnosis is correct. However, the improvement may be short-lived. Commonly used medications include:

Medication	Action	LADA implications
Sulfonylureas First generation: acetohexamide, chlorpropamide, tolazamide, and tolbutamide Second generation: glipizide, glyburide, glimepiride	Stimulate the pancreas to produce insulin.	Stimulation of the beta cells may cause an autoimmune response that hastens the destruction of beta cells and speeds the need for exogenous insulin.
Meglitinides Repaglinide Nateglinide	Stimulate the pancreas to produce insulin.	Same problem as sulfonylureas.
Biguanides Metformin Metformin with glyburide	Reduce production of glucose in the liver	Biguanides do not appear to slow destruction of beta cells, but by controlling glucose levels they may have a protective effect on the beta cells by reducing stimulation.

		Increase risk of lactic acidosis, especially if combined with sulfonylureas.
α-Glucosidase inhibitors Acarbose	Slow intestinal absorption of carbohydrates.	May help reduce overstimulation of beta cells from dietary glucose.
Thiazolidinediones Pioglitazone, rosiglitazone	Improve insulin sensitivity, transport, and utilization.	May have similar protective effect as biguanides, but if insulin resistance is not a problem, they may have little effect.

The approach to treatment for LADA may need to be different from that of diabetes mellitus type 2 because the primary problem is inadequate production of insulin. Thus, medications that improve insulin sensitivity are likely to have little effect even if the person actually has insulin resistance. In fact, failure to respond to these medications and dietary modifications may be an indication that the patient has LADA. However, medications that stimulate the pancreas may show initial improvement but may cause beta cell destruction, so this poses a dilemma. While it seems logical that early treatment of LADA with insulin may be effective in delaying onset of full-blown type 1, in fact, studies have shown there is no benefit to beginning insulin early.

Research is ongoing to determine the best approach to treat LADA. Phase 2 and phase 3 studies are being conducted with vaccine-based therapy to determine if it can preserve endogenous insulin and to investigate long-term effects of the vaccine. Early results are positive in that the vaccine appears to delay destruction of beta cells.

What complications are associated with LADA?

The most common complication of LADA is ketoacidosis related to rising blood glucose levels as insulin production falls and halts, especially if the patient has been misdiagnosed as diabetes mellitus type 2 and is not carefully monitored. Frequent monitoring of blood glucose is especially important as the time between diagnosis and insulin dependency may be relatively short. Diabetic ketoacidosis results when the body breaks down fat (lipolysis) to produce free fatty acids as an alternate energy source to glucose. Glycerol in the liver and in fat cells converts to ketone bodies, and the excess ketone

bodies are excreted through the kidneys and respirations. The ketone bodies lower serum pH, which causes the ketoacidosis.

Symptoms of DKA include:
- Kussmaul respirations with "ketone breath" and hyperventilation.
- Electrolyte and fluid imbalance, including hypokalemia.
- Cardiac dysrhythmias (because of hypokalemia) may cause cardiac arrest.
- Hyperglycemia.

Immediate treatment with insulin infusion and electrolytes is critical to avoid coma and death.

Because LADA is not associated with metabolic syndrome, the hypertension and vascular changes that are common with diabetes mellitus type 2 are less common with LADA. For example, the risk of amputation related to circulatory impairment is highest in those with long-term diabetes mellitus type 2 than those with type 1 or LADA. Other complications typically associated with diabetes mellitus type 1 such as diabetic retinopathy, neuropathy, kidney failure, and blindness may occur with LADA.

Summary

Diabetes mellitus type 1 is characterized by destruction of beta cells in the pancreas and reduced production of insulin. Onset is usually before age 30, and patients progress rapidly from diagnosis to insulin dependency. Diabetes mellitus type 2 is characterized by insulin resistance. Onset is usually during older adulthood, and progression is slow. Latent autoimmune diabetes in adults (LADA) has characteristics of both disorders. Onset is usually between 30 to 50. Beta cells are destroyed, leading to insulin dependency, but this occurs slowly, usually over 2 to 4 years. Insulin resistance may be present but is not the primary problem. The criteria for diagnosis include 1) autoantibodies in the blood, 2) adult onset, and 3) no need for insulin for ≥6 months after onset of symptoms. At present, most people with LADA are misdiagnosed as diabetes mellitus type 2. Autoantibody tests include ICA, GADA, IA-2A and IAA with GADA most diagnostic for LADA. As insulin levels fall, C-peptide levels also drop. Genetic tests indicate that LADA has genetic risk factors in common with both diabetes mellitus, type 1 and type 2. There is as yet no consensus regarding treatment of LADA, but treatment is usually similar to that of diabetes mellitus type 2 although drugs to stimulate production of insulin may, in fact, increase the rate of beta cell destruction. Drugs to combat insulin resistance may not be effective if insulin production is

inadequate. A vaccine to stop destruction of beta cells is in phase 2 and phase 3 trials and shows promise.

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