

## LATENT AUTOIMMUNE DIABETES IN ADULTS (LADA) AND AUTOIMMUNE THYROIDITIS (MINIREVIEW)

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Latent autoimmune diabetes in adults (LADA) is characterised by clinical presentation as type 2 diabetes after 25 years of age, initial control achieved with diet or oral hypoglycaemic agents during at least 6 months, presence of autoantibodies (first of all GADA) and some immunogenetic features of diabetes mellitus type 1. In patients with an autoimmune endocrine disease, which could be also autoimmune diabetes, there is a high risk of development of another autoimmune endocrine disorder. The coexistence of two or more autoimmune endocrine diseases is pathognomonic for autoimmune polyglandular syndrome. Autoimmune thyroiditis and type 1 diabetes mellitus are the most common combination of autoimmune endocrine diseases reported. Most studies reported the prevalence of autoimmune thyroiditis in “typical” type 1 adult diabetic subjects about 20 – 40%. Little is known about the prevalence of autoimmune thyroiditis in subjects with LADA. Only a few studies confirmed a high prevalence of thyroid autoantibodies in type 2 diabetic subjects with GADA compared to type 2 diabetic subjects without GADA and compared to non-diabetic population too.

**Key words:** Diabetes mellitus type 1 – LADA – Autoimmune thyroiditis – Autoimmune polyglandular syndrome

### 1. Latent autoimmune diabetes in adults (LADA)

Latent autoimmune diabetes in adults (LADA) has been characterised in the early 1980s (PITTMAN et al. 1982), however the name LADA is used from 1990s (TUOMI et al. 1993; ZIMMET et al. 1994). The usual patient with LADA is 25 years or older and non-obese, presents with what clinically appears to be type 2 diabetes, and is often maintained in good metabolic control on diet or oral hypoglycaemic therapy for up to several years before insulin dependency (Table 1).

The current classification of diabetes used aetiology-based approach and defined type 1 diabetes mellitus as the disease, that is primarily due to pancreatic beta-cell destruction, usually immune mediated (EXPERT COMMITTEE 1997). The destructive process usually leads to absolute insulin deficiency.

LADA is a special subgroup of diabetes, which could represent a late manifestation of type 1 diabetes. The autoimmune destructive process is much slower, making it sometimes difficult to distinguish clinically between type 1 and type 2 diabetes. The development of clinical symptoms is often insidious, without pathognomonic features typical for type 1 diabetes such as severe polydipsia, polyuria, weight loss or ketoacidosis. However the presence of serological markers of autoimmunity and the presence of certain DR and DQ alleles associated with type 1 diabetes susceptibility in LADA supported the ranking of LADA among autoimmune type 1 diabetes. The other feature of type 1 diabetes insulinopenia is often difficult to demonstrate in adults, because there may be residual beta-cell secretion for years.

It is with the LADA group that problems exist in classification between type 1 and type 2 diabetes in

**Table 1 (according to ZIMMET et al. 1999)**

Features of LADA
Patients usually aged $\geq 25$ years
Clinical presentation “masquerading” as non-obese type 2 diabetes
Initial control achieved with diet alone or diet and oral hypoglycaemic agents
Insulin dependency occurs within months but can take 10 years or more
Other features of type 1 diabetes
Low fasting and post-glucagon stimulated C-peptide
HLA susceptibility alleles
ICA+
GADA+

adults (ZIMMET et al. 1999). The presence of autoantibodies in adult onset diabetes patients is not enough for the classification as LADA (TUOMI et al. 1999). There is still a small group of obese patients with autoimmune markers of insulinitis and higher C-peptide levels and more features of the metabolic syndrome (TUOMI et al. 1999; MARTINKA et al. 2000), which represent the non-progressive form of insulinitis. In this case autoimmune insulinitis is probably not the major pathogenic mechanism of diabetes and it is better to use the expression “type 2 diabetes with GAD antibodies” (TUOMI et al. 1999).

## 2. Autoimmune thyroiditis and type 1 diabetes mellitus

The associated incidence of autoimmune thyroiditis has been studied in the BB/W rat (STERNTHAL et al. 1981) and in the NOD mice (BERNARD et al. 1992), which are useful models for type 1 diabetes as a result of an autoimmune destruction of the beta cells. The incidence of thyroiditis, determined from histological examination of thyroid tissue, was about 59 % in BB/W rats (STERNTHAL et al. 1981) and 70 % in NOD mice (BERNARD et al. 1992). The presence of circulating antibodies to mouse thyroid membrane antigen was demonstrated in 35 % of NOD mice (BERNARD et al. 1992).

On account of the clinical association between diabetes mellitus and autoimmune thyroiditis, there were a lot of studies undertaken in humans to determine the higher prevalence of autoimmune thyroidi-

tis and the higher occurrence of serum anti-thyroid antibodies in type 1 diabetic patients compared with age- and sex-matched non-diabetic subjects. The first studies were performed in the 1960s and the early 1970s and they found significantly higher incidence of thyroid antibodies in juvenile-onset diabetics compared to non-diabetics (LANDING et al. 1963; GOLDSTEIN et al. 1970).

Nowadays the prevalence of autoimmune thyroiditis in children with type 1 diabetes has been estimated from the available data as equalling 4 – 16 % (PAVIA et al. 1989; RADETTI et al. 1995; HANSEN et al. 1999) – the high range is caused by using different diagnostic criteria for autoimmune thyroiditis, which are a combination of presence of thyroid antibodies, thyroid function assessment, ultrasound picture and fine needle biopsy in some studies. Besides, the prevalence of thyroid auto-antibodies increased dramatically with age, this was confirmed in the study of 495 German type 1 diabetic patients, where the prevalence of thyroid antibodies was 3.7 % in patients less than 5 years of age and 25 % in the age group 15-20 years (HOLL et al. 1999).

The frequency of autoimmune thyroiditis in type 1 diabetic adults is higher than in children and equals about 20 – 40 % (PERROS et al. 1995; ABRAMS et al. 1996; VONDRA et al. 1996; MCCANLIES et al. 1998). In more than 50 % of the individuals with autoimmune thyroiditis and type 1 diabetes was demonstrated decreased function of the thyroid gland (MCCANLIES et al. 1998). VONDRA et al. (1996) demonstrated in their 4-years follow-up study of 34 patients significantly higher prevalence of subclinical hypothyroidism in the diabetics with repeatedly detected both antibodies (thyroid peroxidase antibodies and thyroglobulin antibodies) compared to the diabetics with only one (thyroid peroxidase) antibody repeatedly detected: 86 % versus 25 %,  $P < 0.05$  (VONDRA et al. 1996). In all studies in diabetics, it has been confirmed that the female has predominance of autoimmune thyroiditis, which is well known from non-diabetic population.

The clinical relevance of associated autoimmune thyroiditis in type 1 diabetics is undoubted. Unfortunately only a few studies have analysed the possible influence of autoimmune thyroiditis in the clinical presentation and metabolic control of diabetes. Poorer metabolic control of diabetes has been report-

**The occurrence  
(TPOAb)**

Reference	Number Male: Female
HANSEN et al. 1999	105 (55:50)
HOLL et al. 1999	459 (234:261)
ABRAMS et al. 1995	77 (44:33)
ABRAMS et al. 1995	80 (60:20)
FERNANDEZ- CASTANER et al. 1999	111 (63:48)

ed in pregnant type 1 diabetes women with associated autoimmune thyroiditis (FERNANDEZ-SOTO et al. 1997). On the other hand the metabolic control of diabetes in non-pregnant adult diabetics, as reflected by glycosylated haemoglobin levels, did not differ in subjects having coexisting autoimmune thyroiditis and diabetes (McCANLIES et al. 1998; FERNANDEZ-CASTANER et al. 1999).

Although there is a strong association of polymorphism of both the HLA class II DR-DQ genes and the CTLA-4 gene with genetic risk of type 1 diabetes and thyroid diseases (BADENHOOP et al. 1995; DONNER et al. 1997; BARBESINO and CHIOVATO 2000), the support that a common genetic background is responsible for the association of type 1 diabetes mellitus and autoimmune thyroiditis still requires the evaluation using population-based data.

**3. Autoimmune thyroiditis and LADA**

Although many studies have shown the association between autoimmune thyroiditis and type 1 diabetes, little is known of the risk for thyroid autoimmunity in subjects with LADA. The major problem is still the correct classification of diabetes, which is very difficult in adult onset diabetes

and using the cross-section study makes it more complicated.

Some studies have investigated type 2 diabetic patients and divided in groups in relation of presence GADA or requirement of insulin therapy. Finnish authors examined a group of 204 patients with type 2 diabetes who were controlled with diet or oral hypoglycaemic agents and 108 age-matched type 2 diabetes patients who required insulin to control their hyperglycaemia. The insulin requiring diabetics differed in higher frequency of thyroid peroxidase antibodies from non-insulin requiring diabetics: 34 % versus 20 %, P<0.02 (GROOP et al. 1988). In the other Finnish study of 102 patients with diagnosis of type 2 diabetes and >35 years of age at diagnosis were compared GADA-positive to GADA-negative subjects. GADA-positive subjects (n=33.32 %) were found to have a higher prevalence of thyroglobulin antibodies (7 % versus 3 %) and thyroid peroxidase antibodies (28 % versus 19%); however, this difference was not statistically significant (TUOMI et al. 1993). The other study from Italy analysed serum samples from 600 adult subjects with clinical diagnosis of type 2 diabetes mellitus for the presence of thyroid peroxidase antibodies (GAMBELUNGHE et al. 2000). GADA were found in 11 % and thyroid per-

**The occurrence**  
(DM2 =

Reference	Type of di:
Groop et al. 1988	Initial diag after 35 yr:
Groop et al. 1988	DM2 requi therapy
Groop et al. 1988	DM2 non-i insulin the:
Tuomi et al. 1993	Initial diag after 35 yr:
Tuomi et al. 1993	DM2 and GADA-po:

oxidase antibodies occurred more frequently in this group compared to GADA-negative subjects: 24 % versus 5 %,  $P < 0.0001$  (GAMBELUNGHE et al. 2000).

#### 4. Autoimmune polyglandular syndromes

Autoimmune thyroiditis is often associated with type 1 diabetes mellitus. The coexistence of these two autoimmune endocrine diseases is pathognomonic for autoimmune polyglandular syndromes (APS), APS type II or type III respectively. Autoimmune polyglandular syndrome is characterised by the association of two or more endocrine disorders of autoimmune origin, which may coexist with autoimmune disorder in other organs. Two major types of autoimmune polyglandular syndrome were characterised in 1981 by NEUFELD, MACLAREN and BLIZZARD

(1981). Type I APS is associated with chronic mucocutaneous candidiasis and the age of onset is predominately in childhood. The disease is caused by mutation in a single gene called APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy) or AIRE (autoimmune regulator) and shows a penetration of 100% (OBERMAYER-STRAUB and MANNIS 1998). Type II APS and type III APS are characterised by adult onset and they are believed to be polygenic, characterised by dominant inheritance and association with HLA alleles. Type II APS included simultaneous development of Addison disease and thyroid failure whereto type 1 diabetes mellitus occurred in the half of cases. Type III differs from type II in non-presence of Addison disease and the other typical feature is the presence of non-endocrinological autoimmune diseases as vitiligo,

chronic gastritis, pernicious anaemia, alopecia, rheumatological diseases etc. Because of not clear definition and lack of predictive value, the isolation of type III APS from type II APS is questioned. Some authors distinguish only two types (type I and type II) of APS.

There is usually long interval between the onset of various endocrine diseases and they occur in different subsequence. In a study of 151 patients with type II APS was found diabetes mellitus type 1 as the first disease manifested in half of the cases, autoimmune thyroiditis was found as the first manifestation of APS in 17% of the cases (FORSTER et al. 1999). The most common combination was type 1 diabetes with autoimmune thyroid disease in 33% cases (FORSTER et al. 1999).

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