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Distinct clinical and laboratory characteristics of latent autoimmune diabetes in adults in relation to type 1 and type 2 diabetes mellitus

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Abstract

Ever since its first appearance among the multiple forms of diabetes, latent autoimmune diabetes in adults (LADA), has been the focus of endless discussions concerning mainly its existence as a special type of diabetes. In this mini-review, through browsing important peer-reviewed publications, (original articles and reviews), we will attempt to refresh our knowledge regarding LADA hoping to enhance our understanding of this controversial diabetes entity. A unique combination of immunological, clinical and metabolic characteristics has been identified in this group of patients, namely persistent islet cell antibodies, high frequency of thyroid and gastric autoimmunity, DR3 and DR4 human leukocyte antigen haplotypes, progressive loss of beta cells, adult disease onset, normal weight, defective glycaemic control, and without tendency to ketoacidosis. Although anthropomorphic measurements are useful as a first line screening, the detection of C-peptide levels and the presence of glutamic acid decarboxylase (GAD) autoantibodies is undoubtedly the sine qua non condi-

tion for a confirmatory LADA diagnosis. In point of fact, GAD autoantibodies are far from being solely a biomarker and the specific role of these autoantibodies in disease pathogenesis is still to be thoroughly studied. Nevertheless, the lack of diagnostic criteria and guidelines still puzzle the physicians, who struggle between early diagnosis and correct timing for insulin treatment.

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Key words: Latent autoimmune diabetes in adults; Type 1 diabetes mellitus; Type 2 diabetes mellitus; Autoantibodies; Glutamic acid decarboxylase 65

Core tip: A unique combination of, immunological, clinical and metabolic characteristics has been identified in latent autoimmune diabetes in adults (LADA) patients. Even so, the current definition of LADA fails to capture in one snapshot insulin resistance and autoimmunity, this very special pathognomonic characteristic of LADA. Addressing this dual facet of LADA would undoubtedly provide insight into disease pathogenesis and help in the immediate identification and prompt insulin therapy.

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INTRODUCTION

As early as in the end-1970s, Irvine identified a group of patients with diabetes who although treated with oral hypoglycaemic agents, they possessed islet cell antibodies

(ICA)^[1]. Not only had these ICA-positive patients higher prevalence of other organ specific autoantibodies, they showed a significant tendency to progress faster towards insulin deficiency as well. Interestingly, in these patients persistence of ICA for more than five years from diabetes diagnosis was associated with coexistent of organ specific autoimmune disease and with human leukocyte antigen (HLA)-B8, A1 1. The autoimmune signature in these patients lead to be classified as type 1 diabetes (T1D)^[2,3].

Subsequently, a unique combination of immunological, clinical and metabolic characteristics has been identified for this group of patients, namely persistent ICA, high frequency of thyroid and gastric autoimmunity, HLA-DR3 and DR4, progressive loss of beta cells, adult disease onset, normal weight, defective glycaemic control, lower initial levels of C-peptide and impaired response after glucagon stimulation compared to T2D patients, and without tendency to ketoacidosis^[4-8]. But, the idea of latent autoimmune diabetes mellitus in adults has been only recently introduced^[9]. More specifically, in 1994 Paul Zimmet *et al*^[10] and Tuomi *et al*^[11] introduce the term latent autoimmune diabetes in adults (LADA) for LADA and 5 years later the 3 criteria that define LADA are suggested, which are (1) GABA-synthesizing enzyme, glutamic acid decarboxylase (GAD) antibody positivity (> 5 RU); (2) age of diabetes onset > 35 years; and (3) insulin independence at diagnosis (at least 6 mo). However, the current definition of LADA fails to capture in one snapshot insulin resistance and autoimmunity, this very special pathognomonic characteristic of LADA^[12].

On the other hand, the World Health Organisation diabetes classification does not differentiate LADA as a distinct entity^[13]. In fact, the concept of LADA is strongly debated since many researchers question whether LADA is a definite form of diabetes and propose instead that LADA represents slowly evolving T1D which should be regarded as a continuum^[14-16]. Even so, LADA can nicely describe patients with features of both T1D and T2D and provide with a better understanding on the grey zone between these two types^[17-19]. Addressing this dual facet of their disease would undoubtedly facilitate treatment option and therefore benefit LADA patients.

IMMUNOLOGICAL CHARACTERISTICS

Bottazzo was the first to describe the presence of ICAs in T1D patients having also an endocrine disorder of autoimmune etiology. These antibodies were detected by indirect immunofluorescence on pancreatic cryosections and they were named as such because they targeted unknown elements of islet cells^[20].

Nowadays, commercial available kits using pancreas of primate origin are used at routine basis for the determination of ICAs. To facilitate communication among different laboratories and give the possibility of comparable ICA assays, the results should be given in Juvenile Diabetes Foundation units. On the other hand, one should bear in mind that the limitations of ICA assay are

the demanding standardization and challenging interpretation of the results. Despite those restrictions, in the 4th International ICA Workshop it was reported that ICA diagnostic test has exceptional specificity and acceptable concordance among the different laboratories^[21].

There is a bunch of studies addressing the ICAs relevance to T1D. It is now clear that more than 70% newly diagnosed T1D patients are ICA-seropositive^[22]. With a specificity of about 97%, their presence has been reported in less than 4% of healthy subjects^[23]. It should be mentioned that in contrast to general population where ICAs higher than 20 JFD is not of clinical relevance, in the first degree T1D relatives this finding is highly prognostic of T1D^[24,25]. Finally, it is important for clinicians to closely follow up ICA-positive patients who are receiving oral hypoglycaemic agents, since their presence in this population is strongly predictive of switching to insulin dependency^[26].

Anti-insulin autoantibodies (IAAs) were the first specific ICAs to be identified and this was done in 1983 by Palmer *et al*^[27] who performed seminal studies in this area using serum from patients who have not been challenged by exogenous insulin at the time of sample collection. Subsequent research have addressed the insulin levels after glucose challenge and it was concluded that insulinopenia was more prevalent in subjects possessing both, ICAs and IAAs, compared to those being positive just for ICAs^[28]. However, this marker has a relatively low sensitivity, being even less than 40%^[29].

At the 4th International Workshop regarding standardization of IAAs assays it was suggested that RIA should be the method of choice for IAAs determination^[30]. However, in the routine laboratory practice their presence can be also assessed by the enzyme-linked immunosorbent assay (ELISA). A reasonable concern would be how the available assays can distinguish between endogenous and exogenous insulin, but this is feasible through distinct idiotypes^[31].

Notably, IAAs prevalence is actively influenced by both, sex and age. In detail, in young patients there is an equal incidence of IAAs in both sexes which is skewed at 2 males: 1 female in ages greater than 15 years old^[32]. Additionally, these antibodies are inversely correlated with age and since their prevalence sharply drops with age, it is not surprising that they are of low diagnostic value for LADA^[33].

The second ICAs specific target to be identified was the GABA-synthesizing enzyme, GAD, a molecule with a size of 64.000 M(r)^[34]. Two forms of GAD exist in humans, each transcribed by different gene, termed according to their molecular mass GAD65 and GAD67, and the former being the antigenic target for T1D^[35]. Noteworthy, anti-GAD65 autoantibodies are the most typical and prevailing antibodies connected with ICA reactivity^[23]. An interesting proposed aspect on anti-GAD65 autoantibodies is that they are present in healthy individuals but they cannot be detected by conventional methods since they are masked by anti-idiotypic antibodies^[36].

Anti-GAD65 autoantibodies are detected by commercial available RIAs as well as ELISAs and interestingly enough recent ELISAs offer comparable specificity with RIAs and even better sensitivity^[37]. These autoantibodies are positively correlated with age and in the female population are found in greater levels. Serum conversion for these antibodies, from negative to positive, peaks after T1D diagnosis and usually they can be detected even when ICAs becoming gradually undetectable^[23]. Since GAD65 is an intracellular antigen, we speculate that during disease progression islet cells could release GAD65, explaining partially the fact that they can be detected after disease onset. For the aforementioned reasons, anti-GAD65 autoantibodies have major role in the management of diabetes in adults. In fact, their positive predictive value in mid-aged population has been reported to be 50%^[38].

As regard GAD65 autoantibodies in LADA, the Non-Insulin Requiring Autoimmune Diabetes (NIRAD) nationwide survey has shown that anti-GAD65 titres are useful to categorise patients with adult-onset autoimmune diabetes in two different distinct groups with characteristic clinical picture, autoimmune features, and genetic signature. In detail, patients with higher anti-GAD65 titres can be described by a more profound autoimmunity, quite marked dependency on insulin, higher levels of serum A1C, and lower both body mass index (BMI) and metabolic syndrome prevalence and, regarding genetic traits, decreased frequency of HLA-DRB1*0403 and HLA-DQB1*0602 and an increased for HLA-DRB1*03 and HLA-DQB1*0201 characterises the patients with higher anti-GAD65 titres^[39]. Furthermore, studies from the same nationwide survey revealed that in LADA, the variant PTPN22 1858T is strongly associated with high titres of anti-GAD65 autoantibodies while the low levels are correlated to the T2D genetic variant of susceptibility, TCF7L2^[40,41]. It has also been suggested that the presence of high anti-GAD65 titres and/or anti-GAD65 autoantibodies directed against the C-terminal and not the middle epitopes of the protein can group a LADA sub-phenotype with many similarities with classic T1D and a high probability to develop insulin deficiency^[42].

On the other hand, other groups do not rely entirely on high anti-GAD65 titres, in order to predict the progression of LADA. Instead, strong predictors are considered the co-existence of positive autoantibodies and both HLA-DRB1 and HLA-DQB1, while, traits including female gender and low BMI and are highly likely to predict insulin requirement within 4 years post-diagnosis^[43].

In mid-1990s, two independent groups will add an additional T1D specific autoantigen to the ICAs reactivity panel, the insulinoma antigen 2 (IA-2), a transmembrane molecule belonging to the family of protein tyrosine phosphatases^[44-46]. IA-2 is a ubiquitous molecule expressed by neuroendocrine cells, including islet cells of the pancreas, and is localised in the membranes of secretory granules^[47].

Within the framework of T1D diagnostic approach, antibodies against IA-2 can be detected by RIA or ELISA

commercial kits, with both methods giving comparable results^[37]. As a T1D-specific biomarker, anti-IA-2 autoantibodies have a sensitivity of about 60%, meaning that they are less sensitive compared to anti-GAD65 autoantibodies, but when compared to IAA they have higher sensitivity^[29]. In contrast to IAA and ICA, anti-IA-2 AAbs show no variation with age and thus, when anti-GAD65 autoantibodies are also evaluated, an autoimmune signature of the diabetes can be defined^[23].

Recently, antibodies against the IA-2 (256-760) fragment were shown to be a reliable marker in LADA patients and they were positively correlated with higher frequency of autoimmunity and susceptible HLA haplotypes^[48].

Patients with autoimmune diabetes are likely to be presented with an additional autoimmune condition of endocrine (thyroid and adrenal glands) or non-endocrine organs (thyroid and adrenal glands)^[23]. Regarding endocrine organ-specific autoimmune conditions, anti-TPO (thyroid peroxidase)/anti-thyroglobulin (anti-Tg) antibodies, marker for autoimmune thyroid disease can be detected in about one fifth of patients with T1D, while anti-adrenal autoantibodies, marker for Addison's disease are rather less common in T1D, being found in less than 2%^[49,50]. Regarding non-endocrine organs, autoimmune gastritis, characterised by the presence of anti-parietal-cell antibodies can be found in about one tenth of patients with autoimmune diabetes, while celiac disease, characterised by an immunological signature of anti-endomysial, anti-Tg and anti-gliadin antibodies, with a prevalence of 11% is considered to be common in T1D^[50,51].

Regarding organ specific autoantibodies in LADA, the recent NIRAD study 6 suggests a higher frequency of organ-specific antibodies in subjects with high anti-GAD65 titres^[52]. They additionally recommend considering that the risk for the presence of other specific antibodies in LADA depends on both, GAD65 titre and gender, and thus, knowledge of the specific odd ratio can be helpful during screening^[52].

CLINICAL AND METABOLIC CHARACTERISTICS

First and foremost, the mean age at onset is a highly important hand tool for the clinician, who has to decide upon the different type of diabetes and consequently on the appropriate treatment for the patient as quickly as possible. According to study groups, the age of older than 25 years at onset is a supportive finding towards LADA^[19,53]. Furthermore, in comparison to T2D, stimulated as well fasting C-peptide is lower in LADA^[5]. Additionally, the level of insulin secretion in LADA is believed to be intermediate between T1D and T2D 5. Importantly, a fast decline in both insulin secretion and stimulated C-peptide secretion occurs rather fast, namely within a few years after LADA diagnosis^[54]. In patients over 35 years old at diagnosis and duration of diabetes less than 5 years, the presence of diabetes-specific antibodies is related to lower fasting C-peptide, less often neuropathy

and blood pressure closer to the normal values (56). On the other hand, only patients with more than 1 antibody have reduced residual beta-cell function, and only these patients tend to be leaner^[55].

A review by Fournalos *et al*^[54] concludes that patients with LADA are indeed insulin resistant based on homeostasis model assessment, while 50% of insulin secretory failure occurs within the first 4 years. Furthermore, although controversial, in agreement with our observation, LADA patients are presented with lower BMI, blood pressure and triglyceride levels compared to T2D^[56].

Regarding treatment policy in LADA patients, time to insulin treatment is based on clinical judgement, with GAD autoantibodies being of utmost importance^[57]. Interestingly, Stenström *et al*^[58] have suggested that insulin treatment in LADA patients should start as soon as possible. Factually, guidelines on LADA treatment do not exist and is controversial whether sulphonylurea, insulin, vitamin D or alternative therapies such as GAD65, can influence the beta-cell loss progression and metabolic control^[59]. Since LADA patients are presented not only with gradually developing insulin deficiency, but also with insulin resistance, a unique treatment strategy should be designed, in order to treat hyperglycaemia and to preserve b-cell function^[60].

CONCLUSION

There is adequate evidence that LADA constitutes a special form of diabetes, with a unique immunological, metabolic and clinical signature, while its pathognomonic characteristic can be described as latent autoimmunity, combined with glucose resistance. The lack of a consensus amid diabetes experts hampers the uniformity of the studies and perplexes results interpretation. The need of a clear definition, fulfilling the metabolic and immunologic characteristic of the disease, is unambiguously required. Even better, diagnostic criteria and guidelines would facilitate disease management and pave the way for LADA understanding.

REFERENCES

- Irvine WJ, McCallum CJ, Gray RS, Campbell CJ, Duncan LJ, Farquhar JW, Vaughan H, Morris PJ. Pancreatic islet-cell antibodies in diabetes mellitus correlated with the duration and type of diabetes, coexistent autoimmune disease, and HLA type. *Diabetes* 1977; **26**: 138-147 [PMID: 320073 DOI: 10.2337/diab.26.2.138]
- Irvine WJ. Classification of idiopathic diabetes. *Lancet* 1977; **1**: 638-642 [PMID: 66440 DOI: 10.1016/S0140-6736(77)92071-2]
- Di Mario U, Irvine WJ, Borseley DQ, Kyner JL, Weston J, Galfo C. Immune abnormalities in diabetic patients not requiring insulin at diagnosis. *Diabetologia* 1983; **25**: 392-395 [PMID: 6360778 DOI: 10.1007/BF00282516]
- Groop LC, Bottazzo GF, Doniach D. Islet cell antibodies identify latent type I diabetes in patients aged 35-75 years at diagnosis. *Diabetes* 1986; **35**: 237-241 [PMID: 3510930 DOI: 10.2337/diab.35.2.237]
- Gottsäter A, Landin-Olsson M, Fernlund P, Lernmark A, Sundkvist G. Beta-cell function in relation to islet cell antibodies during the first 3 yr after clinical diagnosis of diabetes in type II diabetic patients. *Diabetes Care* 1993; **16**: 902-910 [PMID: 8325204 DOI: 10.2337/diacare.16.6.902]
- Gleichmann H, Zörcher B, Greulich B, Gries FA, Henrichs HR, Betrams J, Kolb H. Correlation of islet cell antibodies and HLA-DR phenotypes with diabetes mellitus in adults. *Diabetologia* 1984; **27** Suppl: 90-92 [PMID: 6383926 DOI: 10.1007/BF00275656]
- Groop L, Miettinen A, Groop PH, Meri S, Koskimies S, Bottazzo GF. Organ-specific autoimmunity and HLA-DR antigens as markers for beta-cell destruction in patients with type II diabetes. *Diabetes* 1988; **37**: 99-103 [PMID: 3275559 DOI: 10.2337/diab.37.1.99]
- Groop LC, Eriksson J, Ekstrand A, Franssila-Kallunki A, Saloranta C, Miettinen A. Metabolic characteristics of autoimmune diabetes mellitus in adults. *Diabetologia* 1991; **34**: 46-51 [PMID: 2055339 DOI: 10.1007/BF00404024]
- Tuomi T, Groop LC, Zimmet PZ, Rowley MJ, Knowles W, Mackay IR. Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease. *Diabetes* 1993; **42**: 359-362 [PMID: 8425674 DOI: 10.2337/diab.42.2.359]
- Zimmet PZ, Tuomi T, Mackay IR, Rowley MJ, Knowles W, Cohen M, Lang DA. Latent autoimmune diabetes mellitus in adults (LADA): the role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. *Diabet Med* 1994; **11**: 299-303 [PMID: 8033530 DOI: 10.1111/j.1464-5491.1994.tb00275.x]
- Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A, Nissén M, Ehrnström BO, Forsén B, Snickars B, Lahti K, Forsblom C, Saloranta C, Taskinen MR, Groop LC. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. *Diabetes* 1999; **48**: 150-157 [PMID: 9892237 DOI: 10.2337/diabetes.48.1.150]
- Redondo MJ. LADA: time for a new definition. *Diabetes* 2013; **62**: 339-340 [PMID: 23349539 DOI: 10.2337/db12-1171]
- Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539-553 [PMID: 9686693]
- Rolandsson O, Palmer JP. Latent autoimmune diabetes in adults (LADA) is dead: long live autoimmune diabetes! *Diabetologia* 2010; **53**: 1250-1253 [PMID: 20336277 DOI: 10.1007/s00125-010-1713-0]
- Gale EA. Latent autoimmune diabetes in adults: a guide for the perplexed. *Diabetologia* 2005; **48**: 2195-2199 [PMID: 16193287 DOI: 10.1007/s00125-005-1954-5]
- Hawa MI, Kolb H, Schloot N, Beyan H, Paschou SA, Buz-zetti R, Mauricio D, De Leiva A, Yderstraede K, Beck-Neilsen H, Tuomilehto J, Sarti C, Thivolet C, Hadden D, Hunter S, Scherthaner G, Scherbaum WA, Williams R, Brophy S, Pozzilli P, Leslie RD. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. *Diabetes Care* 2013; **36**: 908-913 [PMID: 23248199 DOI: 10.2337/dc12-0931]
- Groop L, Tuomi T, Rowley M, Zimmet P, Mackay IR. Latent autoimmune diabetes in adults (LADA)--more than a name. *Diabetologia* 2006; **49**: 1996-1998 [PMID: 16819610 DOI: 10.1007/s00125-006-0345-x]
- Clark A, Desai M. Comment on: Gale EAM (2005) Latent autoimmune diabetes in adults: a guide for the perplexed. *Diabetologia* 48: 2195-2199. *Diabetologia* 2006; **49**: 2222-2224 [PMID: 16832661 DOI: 10.1007/s00125-006-0347-8]
- Appel SJ, Wadas TM, Rosenthal RS, Ovalle F. Latent autoimmune diabetes of adulthood (LADA): an often misdiagnosed type of diabetes mellitus. *J Am Acad Nurse Pract* 2009; **21**: 156-159 [PMID: 19302691 DOI: 10.1111/j.1745-7599.2009.0399.x]
- Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendo-

- crine deficiencies. *Lancet* 1974; **2**: 1279-1283 [PMID: 4139522 DOI: 10.1016/S0140-6736(74)90140-8]
- 21 **Greenbaum CJ**, Palmer JP, Nagataki S, Yamaguchi Y, Moleenaar JL, Van Beers WA, MacLaren NK, Lernmark A. Improved specificity of ICA assays in the Fourth International Immunology of Diabetes Serum Exchange Workshop. *Diabetes* 1992; **41**: 1570-1574 [PMID: 1446798 DOI: 10.2337/diab.41.12.1570]
 - 22 **Atkinson MA**, Maclaren NK. Islet cell autoantigens in insulin-dependent diabetes. *J Clin Invest* 1993; **92**: 1608-1616 [PMID: 8408615 DOI: 10.1172/JCI116745]
 - 23 **Tsirogianni A**, Pipi E, Soufleros K. Specificity of islet cell autoantibodies and coexistence with other organ specific autoantibodies in type 1 diabetes mellitus. *Autoimmun Rev* 2009; **8**: 687-691 [PMID: 19217947 DOI: 10.1016/j.autrev.2009.02.019]
 - 24 **Knip M**, Karjalainen J, Akerblom HK. Islet cell antibodies are less predictive of IDDM among unaffected children in the general population than in sibs of children with diabetes. The Childhood Diabetes in Finland Study Group. *Diabetes Care* 1998; **21**: 1670-1673 [PMID: 9773728 DOI: 10.2337/diabetes.21.10.1670]
 - 25 **Bingley PJ**, Bonifacio E, Shattock M, Gillmor HA, Sawtell PA, Dunger DB, Scott RD, Bottazzo GF, Gale EA. Can islet cell antibodies predict IDDM in the general population? *Diabetes Care* 1993; **16**: 45-50 [PMID: 8422831 DOI: 10.2337/diabetes.16.1.45]
 - 26 **Irvine WJ**, Sawers JS, Feek CM, Prescott RJ, Duncan LJ. The value of islet cell antibody in predicting secondary failure of oral hypoglycaemic agent therapy in Diabetes mellitus. *J Clin Lab Immunol* 1979; **2**: 23-26 [PMID: 95802]
 - 27 **Palmer JP**, Asplin CM, Clemons P, Lyen K, Tatpati O, Raghu PK, Paquette TL. Insulin antibodies in insulin-dependent diabetics before insulin treatment. *Science* 1983; **222**: 1337-1339 [PMID: 6362005 DOI: 10.1126/science.6362005]
 - 28 **Atkinson MA**, Maclaren NK, Riley WJ, Winter WE, Fisk DD, Spillar RP. Are insulin autoantibodies markers for insulin-dependent diabetes mellitus? *Diabetes* 1986; **35**: 894-898 [PMID: 3525287 DOI: 10.2337/diab.35.8.894]
 - 29 **Bingley PJ**, Bonifacio E, Mueller PW. Diabetes Antibody Standardization Program: first assay proficiency evaluation. *Diabetes* 2003; **52**: 1128-1136 [PMID: 12716742 DOI: 10.2337/diabetes.52.5.1128]
 - 30 **Greenbaum CJ**, Palmer JP, Kuglin B, Kolb H. Insulin autoantibodies measured by radioimmunoassay methodology are more related to insulin-dependent diabetes mellitus than those measured by enzyme-linked immunosorbent assay: results of the Fourth International Workshop on the Standardization of Insulin Autoantibody Measurement. *J Clin Endocrinol Metab* 1992; **74**: 1040-1044 [PMID: 1569152]
 - 31 **Devendra D**, Galloway TS, Horton SJ, Evenden A, Keller U, Wilkin TJ. The use of phage display to distinguish insulin autoantibody (IAA) from insulin antibody (IA) idiotypes. *Diabetologia* 2003; **46**: 802-809 [PMID: 12783163 DOI: 10.1007/s00125-003-1107-7]
 - 32 **Williams AJ**, Norcross AJ, Dix RJ, Gillespie KM, Gale EA, Bingley PJ. The prevalence of insulin autoantibodies at the onset of Type 1 diabetes is higher in males than females during adolescence. *Diabetologia* 2003; **46**: 1354-1356 [PMID: 13680123 DOI: 10.1007/s00125-003-1197-2]
 - 33 **Falorni A**, Brozzetti A. Diabetes-related antibodies in adult diabetic patients. *Best Pract Res Clin Endocrinol Metab* 2005; **19**: 119-133 [PMID: 15826926]
 - 34 **Baekkeskov S**, Aanstoot HJ, Christgau S, Reetz A, Solimena M, Cascalho M, Folli F, Richter-Olesen H, De Camilli P. Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. *Nature* 1990; **347**: 151-156 [PMID: 1697648 DOI: 10.1038/347151a0]
 - 35 **Hagopian WA**, Michelsen B, Karlsen AE, Larsen F, Moody A, Grubin CE, Rowe R, Petersen J, McEvoy R, Lernmark A. Autoantibodies in IDDM primarily recognize the 65,000-M(r) rather than the 67,000-M(r) isoform of glutamic acid decarboxylase. *Diabetes* 1993; **42**: 631-636 [PMID: 8454115 DOI: 10.2337/diab.42.4.631]
 - 36 **Oak S**, Gilliam LK, Landin-Olsson M, Törn C, Kockum I, Pennington CR, Rowley MJ, Christie MR, Banga JP, Hampe CS. The lack of anti-idiotypic antibodies, not the presence of the corresponding autoantibodies to glutamate decarboxylase, defines type 1 diabetes. *Proc Natl Acad Sci USA* 2008; **105**: 5471-5476 [PMID: 18367670 DOI: 10.1073/pnas.0800578105]
 - 37 **Rahmati K**, Lernmark A, Becker C, Foltyn-Zadura A, Larsson K, Ivarsson SA, Törn C. A comparison of serum and EDTA plasma in the measurement of glutamic acid decarboxylase autoantibodies (GADA) and autoantibodies to islet antigen-2 (IA-2A) using the RSR radioimmunoassay (RIA) and enzyme linked immunosorbent assay (ELISA) kits. *Clin Lab* 2008; **54**: 227-235 [PMID: 18942490]
 - 38 **Turner R**, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, Shattock M, Bottazzo GF, Holman R. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. *Lancet* 1997; **350**: 1288-1293 [PMID: 9357409]
 - 39 **Buzzetti R**, Di Pietro S, Giaccari A, Petrone A, Locatelli M, Suraci C, Capizzi M, Arpi ML, Bazzigaluppi E, Dotta F, Bosi E. High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. *Diabetes Care* 2007; **30**: 932-938 [PMID: 17392553]
 - 40 **Petrone A**, Suraci C, Capizzi M, Giaccari A, Bosi E, Tiberti C, Cossu E, Pozzilli P, Falorni A, Buzzetti R. The protein tyrosine phosphatase nonreceptor 22 (PTPN22) is associated with high GAD antibody titer in latent autoimmune diabetes in adults: Non Insulin Requiring Autoimmune Diabetes (NIRAD) Study 3. *Diabetes Care* 2008; **31**: 534-538 [PMID: 18056891]
 - 41 **Zampetti S**, Spoletini M, Petrone A, Capizzi M, Arpi ML, Tiberti C, Di Pietro S, Bosi E, Pozzilli P, Giorgino F, Buzzetti R. Association of TCF7L2 gene variants with low GAD autoantibody titre in LADA subjects (NIRAD Study 5). *Diabet Med* 2010; **27**: 701-704 [PMID: 20546291 DOI: 10.1111/j.1464-5491.2010.02997.x]
 - 42 **Falorni A**, Calcinaro F. Autoantibody profile and epitope mapping in latent autoimmune diabetes in adults. *Ann N Y Acad Sci* 2002; **958**: 99-106 [PMID: 12021088]
 - 43 **Maioli M**, Pes GM, Delitala G, Puddu L, Falorni A, Tolu F, Lampis R, Orrù V, Secchi G, Cicalò AM, Floris R, Madau GF, Pilosu RM, Whalen M, Cucca F. Number of autoantibodies and HLA genotype, more than high titers of glutamic acid decarboxylase autoantibodies, predict insulin dependence in latent autoimmune diabetes of adults. *Eur J Endocrinol* 2010; **163**: 541-549 [PMID: 20603341 DOI: 10.1530/EJE-10-0427]
 - 44 **Lan MS**, Wasserfall C, Maclaren NK, Notkins AL. IA-2, a transmembrane protein of the protein tyrosine phosphatase family, is a major autoantigen in insulin-dependent diabetes mellitus. *Proc Natl Acad Sci USA* 1996; **93**: 6367-6370 [PMID: 8692821]
 - 45 **Payton MA**, Hawkes CJ, Christie MR. Relationship of the 37,000- and 40,000-M(r) tryptic fragments of islet antigens in insulin-dependent diabetes to the protein tyrosine phosphatase-like molecule IA-2 (ICA512). *J Clin Invest* 1995; **96**: 1506-1511 [PMID: 7657822 DOI: 10.1172/JCI118188]
 - 46 **Rabin DU**, Pleasic SM, Shapiro JA, Yoo-Warren H, Oles J, Hicks JM, Goldstein DE, Rae PM. Islet cell antigen 512 is a diabetes-specific islet autoantigen related to protein tyrosine phosphatases. *J Immunol* 1994; **152**: 3183-3188 [PMID: 8144912]
 - 47 **Solimena M**, Dirkx R, Hermel JM, Pleasic-Williams S, Shapiro JA, Caron L, Rabin DU. ICA 512, an autoantigen of type I diabetes, is an intrinsic membrane protein of neurosecretory granules. *EMBO J* 1996; **15**: 2102-2114 [PMID: 8641276]
 - 48 **Tiberti C**, Giordano C, Locatelli M, Bosi E, Bottazzo GF, Buz-

- zetti R, Cucinotta D, Galluzzo A, Falorni A, Dotta F. Identification of tyrosine phosphatase 2(256-760) construct as a new, sensitive marker for the detection of islet autoimmunity in type 2 diabetic patients: the non-insulin requiring autoimmune diabetes (NIRAD) study 2. *Diabetes* 2008; **57**: 1276-1283 [PMID: 18332100 DOI: 10.2337/db07-0874]
- 49 **Yu L**, Brewer KW, Gates S, Wu A, Wang T, Babu SR, Gottlieb PA, Freed BM, Noble J, Erlich HA, Rewers MJ, Eisenbarth GS. DRB1*04 and DQ alleles: expression of 21-hydroxylase autoantibodies and risk of progression to Addison's disease. *J Clin Endocrinol Metab* 1999; **84**: 328-335 [PMID: 9920103]
- 50 **De Block CE**, De Leeuw IH, Bogers JJ, Pelckmans PA, Ieven MM, Van Marck EA, Van Acker KL, Van Gaal LF. Autoimmune gastropathy in type 1 diabetic patients with parietal cell antibodies: histological and clinical findings. *Diabetes Care* 2003; **26**: 82-88 [PMID: 12502662]
- 51 **Fröhlich-Reiterer EE**, Hofer S, Kaspers S, Herbst A, Koronouri O, Schwarz HP, Schober E, Grabert M, Holl RW. Screening frequency for celiac disease and autoimmune thyroiditis in children and adolescents with type 1 diabetes mellitus--data from a German/Austrian multicentre survey. *Pediatr Diabetes* 2008; **9**: 546-553 [PMID: 18713134 DOI: 10.1111/j.1399-5448.2008.00435.x]
- 52 **Zampetti S**, Capizzi M, Spoletini M, Campagna G, Leto G, Cipolloni L, Tiberti C, Bosi E, Falorni A, Buzzetti R. GADA titer-related risk for organ-specific autoimmunity in LADA subjects subdivided according to gender (NIRAD study 6). *J Clin Endocrinol Metab* 2012; **97**: 3759-3765 [PMID: 22865904 DOI: 10.1210/jc.2012-2037]
- 53 **Naik RG**, Brooks-Worrell BM, Palmer JP. Latent autoimmune diabetes in adults. *J Clin Endocrinol Metab* 2009; **94**: 4635-4644 [PMID: 19837918 DOI: 10.1210/jc.2009-1120]
- 54 **Fourlanos S**, Dotta F, Greenbaum CJ, Palmer JP, Rolandsson O, Colman PG, Harrison LC. Latent autoimmune diabetes in adults (LADA) should be less latent. *Diabetologia* 2005; **48**: 2206-2212 [PMID: 16193284 DOI: 10.1007/s00125-005-1960-7]
- 55 **Lohmann T**, Kellner K, Verlohren HJ, Krug J, Steindorf J, Scherbaum WA, Seissler J. Titre and combination of ICA and autoantibodies to glutamic acid decarboxylase discriminate two clinically distinct types of latent autoimmune diabetes in adults (LADA). *Diabetologia* 2001; **44**: 1005-1010 [PMID: 11484077 DOI: 10.1007/s001250100602]
- 56 **Scherthaner G**, Hink S, Kopp HP, Muzyka B, Streit G, Kroiss A. Progress in the characterization of slowly progressive autoimmune diabetes in adult patients (LADA or type 1.5 diabetes). *Exp Clin Endocrinol Diabetes* 2001; **109** Suppl 2: S94-108 [PMID: 11460597 DOI: 10.1055/s-2001-18573]
- 57 **Brophy S**, Yderstraede K, Mauricio D, Hunter S, Hawa M, Pozzilli P, Scherthaner G, Schloot N, Buzzetti R, Davies H, Leslie D, Williams R. Time to insulin initiation cannot be used in defining latent autoimmune diabetes in adults. *Diabetes Care* 2008; **31**: 439-441 [PMID: 18083788]
- 58 **Stenström G**, Gottsäter A, Bakhtadze E, Berger B, Sundkvist G. Latent autoimmune diabetes in adults: definition, prevalence, beta-cell function, and treatment. *Diabetes* 2005; **54** Suppl 2: S68-S72 [PMID: 16306343]
- 59 **Brophy S**, Davies H, Mannan S, Brunt H, Williams R. Interventions for latent autoimmune diabetes (LADA) in adults. *Cochrane Database Syst Rev* 2011; (9): CD006165 [PMID: 21901702 DOI: 10.1002/14651858.CD006165.pub3]
- 60 **Hwangbo Y**, Kim JT, Kim EK, Khang AR, Oh TJ, Jang HC, Park KS, Kim SY, Lee HK, Cho YM. Prevalence and clinical characteristics of recently diagnosed type 2 diabetes patients with positive anti-glutamic Acid decarboxylase antibody. *Diabetes Metab J* 2012; **36**: 136-143 [PMID: 22540050 DOI: 10.4093/dmj.2012.36.2.136]

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