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Latent autoimmune diabetes in adults (LADA)

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CONTENTS

Abstract

Latent autoimmune diabetes in adults (LADA) is an autoimmune form of diabetes that presents with circulating autoantibodies, is slowly progressive and does not initially require insulin therapy. Although it has been questioned whether LADA represents a separate disease, a transition phase between type 1 and type 2 diabetes, or just a form of type 1 diabetes, there is a subset of diabetic patients with unique characteristics who may benefit from tailored treatments for this condition.

Introduction

Latent autoimmune diabetes in adults (LADA) is the term that was coined to describe a condition that, although phenotypically identical to type 2 diabetes, also features circulating pancreatic islet cell antibodies (ICAs) and a slow progression to autoimmune β-cell failure (1). Thus, LADA shares features with both type 1 and type 2 diabetes. The acronynm LADA has generally been surrounded by controversy since it has been difficult to define the disorder as a distinct etiological entity and not a mere subtype of type 1 diabetes (2, 3). The term latent has also been questioned, as the disease is not typically latent (i.e., existing but not yet apparent) since autoimmune serology is present and is required for diagnosis (4). Therefore, other acronyms and names have been proposed, such as ADA (autoimmune diabetes in adults) or autoimmune diabetes not requiring insulin at diagnosis, among others (1). Regardless of the term used, the diagnosis of LADA is based on three criteria: 1) diabetes onset occurs at adult age (25-40 years); 2) the presence of circulating ICAs; and 3) insulin therapy is not required for at least 6 months after diagnosis. The serology of LADA patients at diagnosis typically shows circulating islet cell antibodies of the IgG type and antibodies to glutamic acid decarboxylase (GAD), the presence of which has been correlated with further insulin dependence (5). Moreover, the clinical picture of LADA patients may be associated with titers of diabetes-associated autoantibodies, as some authors have proposed. Thus, combined anti-GAD/ICA positivity and/or high-titer anti-GAD was found to correlate with an early age of onset, reduced β-cell function, the presence of other autoimmune disorders, fewer markers of metabolic syndrome (high body mass index, hypertension, dyslipidemia) and increased frequency of high-risk diabetes type 1-associated HLA class II alleles (discussed below) (6).

Clinical symptoms

As mentioned earlier, LADA shares metabolic features with type 1 and type 2 diabetes. Thus, type 2 diabetes and LADA patients have been shown to present with a similar degree of insulin resistance and elevated glucagon levels, but the latter exhibit severe and progressive defects in β-cell function, hence resembling type 1 diabetes (7, 8). However, unique clinical features may be associated with this form of diabetes. Fourlanos et al. found that, compared to patients with type 2 diabetes, most patients with LADA exhibited at least two of the following five clinical parameters: 1) age of onset < 50 years; 2) acute symptoms; 3) body mass index (BMI) < 25 kg/m^2; 4) personal history of autoimmune disease; or 5) family history of autoimmune disease. Moreover, the presence of at least two of these features at diagnosis had a sensitivity and specificity for LADA detection of 90% and 70%, respectively. Alternatively, the presence of less than two distinguishing clinical parameters resulted in a negative predictive value of 99%, hence representing a highly reliable method for excluding the disease (9). When compared to type 1 diabetes patients, LADA subjects have been noted to show higher BMI, elevated triglycerides and HDL cholesterol, greater insulin resistance, as well as greater plasma C-peptide concentrations, an indicator of insulin production by β-cells (10).

The criterion of insulin independence in LADA can be rather subjective and may depend on insulin-prescribing trends, among other factors. A recent study showed that

the time to insulin treatment depended on whether autoantibody testing was performed or not, thus being shorter in those centers that routinely performed laboratory tests for diabetes-associated autoantibodies (11).

Pathophysiology of LADA

The loss of tolerance to self-antigens present in insulin-secreting β-cells in pancreatic islets appears to be the underlying pathogenic process in LADA, as well as in type 1 diabetes. However, both LADA and type 1 diabetes present with specific serological markers. The four islet antibody subtypes, namely ICAs, GAD antibodies, insulinoma antigen 2 (IA-2) antibodies and insulin autoantibodies, are also present in type 1 diabetes, whereas IA-2 and insulin autoantibodies are rarely seen in LADA patients (12). Detection of ICAs and GAD antibodies is thus key in the diagnosis of LADA. The enzyme GAD has two isoforms, GAD65 and GAD67, which catalyze the formation of γ-aminobutyric acid (GABA) in neurons and pancreatic Langerhans islets. The GAD65 isoform appears to be particularly important in the detection of type 1 diabetes, since it is found in up to 80% of patients and is considered a predictive marker (13). GAD65 antibodies appear to bind specific epitopes comprised in the *N*-terminal region of the GAD enzyme (the membrane-anchoring site), according to a study in patients with "slowly progressive type 1 diabetes" (14). In contrast, GAD65 antibodies from the sera of type 1 diabetes patients did not react with this specific *N*-terminal site. Moreover, *N*-terminal binding by GAD65 antibodies was inversely correlated with the time to insulin requirement. However, reactivity against *C*-terminal and middle epitopes of GAD65 has also been described in LADA patients, with no relationship found between binding and time to treatment or disease progression (15). This study confirmed the long-term persistence of GAD antibodies (6 years) after diagnosis, indicating that it is a valid criterion for the diagnosis of LADA several years after the onset of hyperglycemia.

Genetics

Similarly to what occurs in type 1 diabetes, certain HLA class II genes appear to be associated with higher LADA risk. Particularly, HLA DR3 and/or DR4 and DQ2 and/or DQ8 are the highest-risk HLA alleles for type 1 diabetes, which have also been found in LADA patients (4), hence suggesting a similar genetic basis. For instance, LADA and type 1 diabetes patients exhibited an increased prevalence of the high-risk HLA-DQB1*0302, -DR4, -D3 and -DR3/DR4 genotypes and the high-risk DR3/DR4-DQB1*0302 haplotype compared to a control population (16). Interestingly, another study evaluating the genotypes of patients with LADA and nondiabetic individuals found that DR4 antigen specificity subtypes may confer a differential risk for LADA, with DRB1*0401 and DRB1*0403(06/07) being predisposing and protective, respectively (17).

Besides HLA genes, LADA has also been associated with other genetic factors. Thus, variations in the variable number of tandem repeats (VNTR) minisatellite upstream of the insulin gene region *IDDM2*, which accounts for about 10% of familial risk for type 1 diabetes, have also been significantly associated with susceptibility to LADA (18). However, these genetic variations did not help to distinguish between type 1 diabetes and LADA.

Also, outside the HLA region, the tyrosine-protein phosphatase non-receptor type 22 gene (*PTPN22*) encoding a lymphoid-specific phosphatase known as LyP, which is a powerful inhibitor of T-cell activation, has been identified with type 1 diabetes in young subjects (19). A recent study has demonstrated an association between the *PTPN22* C1858T gene polymorphism and patients with adult-onset diabetes and high GAD antibody titers, compared to those with low antibody titers, type 2 diabetes and a control population (20). Other authors have encountered a higher frequency of the C1858T gene polymorphism in LADA patients compared to type 1 diabetes and nondiabetic subjects (21, 22). The *PTPN22* C1858T gene variant has also been linked to other autoantibody-producing autoimmune diseases (23).

A recent study confirmed these findings and showed that LADA shared genetic features with type 1 diabetes, namely associations with HLA-DQB1, insulin gene (*INS*) VNTR and *PTPN22*, but LADA patients also presented with a variant of the transcription factor 7-like 2 (*TCF7L2*) gene, which is strongly associated with type 2 diabetes (24). The authors concluded that these results support the hypothesis that LADA is a combination of type 1 and type 2 diabetes, rather than just a form of type 1 diabetes.

Another study investigated the potential relationship of LADA with cytokine genes involved in the pathogenesis of other autoimmune disorders and found an increased frequency in the interleukin *IL10-1082A/G* gene variant in LADA compared to type 2 diabetics (25). Other studies have shown associations of LADA with insulin resistance genes (*IRS1*, *IRS2*) (26) and vitamin D receptor (*VDR*) gene polymorphisms (27).

Treatment

In general, the treatment of LADA, as well as the major diabetes types, is aimed at providing optimal glycemic control and preserving β-cell function. However, it is not yet clear which are the best treatments for this condition (28). Lifestyle intervention (diet and exercise) together with insulin therapy is usually the strategy of choice. Although efficacy for early insulin treatment (at diagnosis) in preventing β-cell failure has been reported (29), some evidence suggests that it may not be superior to diet or oral hypoglycemic control (30). A randomized, open study is currently examining the clinical efficacy of early insulin treatment in patients with LADA compared to oral hypoglycemic agents (metformin, sulfonylureas, rosiglitazone) (31).

The efficacy of thiazolidinedione treatment in LADA has not been thoroughly studied. Nevertheless, a pilot

Table I: Summary of therapeutic strategies in LADA.

Drug	Design	Treatments	N	Conclusions/Objectives	Ref.
Rosiglitazone	Randomized Unblinded	Rosiglitazone, 4 mg/d + Insulin, b.i.d Insulin, b.i.d.	23	In comparison with insulin monotherapy, combined insulin plus rosiglitazone treatment preserved β-cell residual function at 12 and 18 months of follow-up. No severe hypoglycemic attacks or other adverse events were reported during the study period.	32
Human recombinant GAD65	Randomized Double-blind	Human recombinant GAD65, 20 μg s.c. at wks 1 and 4 Placebo	160	This phase II/III study will investigate the safety and efficacy of Diamyd® (rhGAD65) for the treatment of LADA. The primary outcome measure will assess the change in glycosylated hemoglobin (HbA1c) at 18 months (main study period) after the prime injection of Diamyd® 20 μg versus baseline in comparison with placebo.	33
	Randomized Double-blind	Human recombinant GAD65, 4, 20, 100 or 500 μg s.c. at wks 1 and 4 Placebo	47	This randomized, double-blind, dose-escalation trial of Diamyd® showed increased C-peptide levels at 24 weeks at a dose of 20 μg in LADA patients. No safety issues were reported.	34
DiaPep277	Randomized Double-blind	DiaPep277, s.c. Placebo	100	This study will assess the safety, immunological and clinical efficacy of DiaPep277 versus placebo. DiaPep277 will be administered at 0, 1 and 3 months, and then every 3 months for a total of 8 administrations. The duration of the trial will be 18 months of treatment plus 6 months of follow-up.	36

study evaluating 23 LADA patients randomized to receive premixed human insulin twice daily alone or rosiglitazone (4 mg/day) plus insulin found that this latter approach may be more effective in preserving β-cell function than insulin alone. Combined insulin and rosiglitazone treatment stabilized C-peptide levels after glucose load (PCP) and glucagon-stimulated Δ C-peptide (ΔCP) at 12 and 18 months after treatment onset, while both parameters declined with insulin monotherapy at those time points (32) (Table I).

Current investigations are focusing on two vaccine candidates, which attempt to provide better prevention of islet β-cell destruction (Table I). Diamyd® is a recombinant human DNA vaccine consisting of the recombinant human GAD 65-kD isoform (rhGAD65) that is currently in phase II/III clinical trials for the subcutaneous (s.c.) treatment of type 2 diabetes at Diamyd Medical, and in phase III trials for the treatment of children and adolescents with type 1 diabetes, also as an s.c. formulation. In addition, s.c. administration of rhGAD65 will be examined in a randomized, placebo-controlled, multicenter phase II/III study for the treatment of LADA that is expected to enroll 160 patients. The primary endpoint will be the change in glycosylated hemoglobin (HbA1c) at 18 months (main study period) after the prime injection of Diamyd® 20 μg versus baseline in comparison to placebo. Secondary outcome measures include the change in C-peptide levels, the proportion of patients becoming insulin-dependent and safety variables (33). Preliminary results of a randomized, double-blind, dose-escalation trial of Diamyd® in 47 LADA patients showed increased C-peptide levels at 24 weeks at a dose of 20 μg (34).

DiaPep277 is a synthetic version of the p277 peptide derived from the 60-kDa heat shock protein (HSP60), which represents one of the known β-cell target self-antigens in type 1 diabetes. In nonobese diabetic (NOD) mice, as well as in type 1 diabetic patients, injection of p277 appeared to preserve endogenous insulin production, which may be due to a change in T-cell autoimmunity (from Th1 to Th2 cytokines) (35). In addition to type 1 diabetes, DiaPep277 is currently being evaluated by DeveloGen for the treatment of LADA in a phase II study that will examine the safety and tolerability, as well as the immunological and clinical efficacy of DiaPep277. This study is estimated to recruit 100 patients who will be randomly assigned to DiaPep277 or placebo (36).

References

1. Stenstrom, G., Gottsater, A., Bakhtadze, E., Berger, B., Sundkvist, G. *Latent autoimmune diabetes in adults. Definition, prevalence, beta cell function, and treatment.* Diabetes 2005, 54(Suppl. 2): S68-72.

2. Gale, E.A.M. *Latent autoimmune diabetes in adults: A guide for the perplexed.* Diabetologia 2005, 48(11): 2195-9.

3. Palmer, J.P., Hampe, C.S., Chiu, H., Goel, A., Brooks-Worrell, B.M. *Is latent autoimmune diabetes in adults distinct from type 1*

diabetes or just type 1 diabetes at an older age? Diabetes 2005, 54(Suppl. 2): S62-7.

4. Fourlanos, S., Dotta, F., Greenbaum, C.J., Palmer, J.P., Rolandsson, O., Colman, P.G., Harrison, L.C. *Latent autoimmune diabetes in adults (LADA) should be less latent*. Diabetologia 2005, 48(11): 2206-12.

5. Littorin, B., Sundkvist, G., Hagopian, W. et al. *Islet cell and glutamic acid decarboxylase antibodies present at diagnosis of diabetes predict the need for insulin treatment*. Diabetes Care 1999, 22(3): 409-12.

6. van Deutekom, A.W., Heine, R.J., Simsek, S. *The islet autoantibody titres: Their clinical relevance in latent autoimmune diabetes in adults (LADA) and the classification of diabetes mellitus.* Diabet Med 2008, 25(2): 117-24.

7. Carlsson, A., Sundkvist, G., Groop, L., Tuomi, T. *Insulin and glucagon secretion in patients with slowly progressing autoimmune diabetes (LADA).* J Clin Endocrinol Metab 2000, 85(1): 76-80.

8. Chiu, H.K., Tsai, E.C., Juneja, R., Stoever, J., Brooks-Worrell, B., Goel, A., Palmer, J.P. *Equivalent insulin resistance in latent autoimmune diabetes in adults (LADA) and type 2 diabetic patients*. Diabetes Res Clin Pract 2007, 77(2): 237-44.

9. Fourlanos, S., Perry, C., Stein, M.S., Stankovich, J., Harrison, L.C., Colman, P.G. *A clinical screening tool identifies autoimmune diabetes in adults.* Diabetes Care 2006, 29(5): 970-5.

10. Rosário, P.W., Reis, J.S., Amim, R., Fagundes, T.A., Calsolari, M.R., Silva, S.C., Purisch, S. *Comparison of clinical and laboratory characteristics between adult-onset type 1 diabetes and latent autoimmune diabetes in adults.* Diabetes Care 2005, 28(7): 1803-4.

11. Brophy, S., Yderstræde, K., Mauricio, D. et al. *Time to insulin initiation cannot be used in defining latent autoimmune diabetes in adults*. Diabetes Care 2008, 31(3): 439-41.

12. Seissler, J., Sonnaville, J.J.J., Morgenthaler, N.G. et al. *Immunological heterogeneity in type 1 diabetes: Presence of distinct autoantibody patterns in patients with acute onset and slowly progressive disease.* Diabetologia 1998, 41(8): 891-7.

13. Hinke, S.A. *Finding GAD: Early detection of ß-cell injury*. Endocrinology 2007, 148(10): 4568-71.

14. Kobayashi, T., Tanaka, S., Okubo, M., Nakanishi, K., Murase, T., Lernmark, A. *Unique epitopes of glutamic acid decarboxylase autoantibodies in slowly progressive type 1 diabetes*. J Clin Endocrinol Metab 2003, 88(10): 4768-75.

15. Desai, M., Cull, C.A., Horton, V.A. et al. *GAD autoantibodies and epitope reactivities persist after diagnosis in latent autoimmune diabetes in adults but do not predict disease progression: UKPDS 77.* Diabetologia 2007, 50(10): 2052-60.

16. Hosszúfalusi, N., Vatay, A., Rajczy, K. et al. *Similar genetic features and different islet cell autoantibody pattern of latent autoimmune diabetes in adults (LADA) compared with adult-onset type 1 diabetes with rapid progression*. Diabetes Care 2003, 26(2): 452-7.

17. Desai, M., Zeggini, E,. Horton, V.A. et al. *An association analysis of the HLA gene region in latent autoimmune diabetes in adults.* Diabetologia 2007, 50(1): 68-73.

18. Desai, M., Zeggini, E., Horton, V.A. et al. *The variable number of tandem repeats upstream of the insulin gene is a susceptibility locus for latent autoimmune diabetes in adults.* Diabetes 2006, 55(6): 1890-4.

19. Bottini, N., Musumeci, L., Alonso, A. et al. *A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes*. Nat Genet 2004, 36(4): 337-8.

20. Petrone, A., Suraci, C., Capizzi, M. et al. *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(3): 534-8.

21. Szelachowska, M., Szepietowska, B., Okruszko, A., Wawrusiewicz-Kurylonek, N., Gorska, M., Kretowski, A. *The functional polymorphism (1858/CT) in the PTPN22 gene is associated with late autoimmune diabetes in adults – LADA.* Diabetologia 2006, 49(Suppl. 1): Abst 0295.

22. Tikhonova, T., Shtandel, S., Fedetz, M. et al. *Association of (C1858T) polymorphism in the PTPN22 gene and latent autoimmune diabetes in adults (LADA) at Ukranian population*. 44th Annu Meet Eur Assoc Study Diabetes (EASD) (Sept 7-11, Rome) 2008, Abst 270.

23. Criswell, L.A., Pfeiffer, K.A., Lum, R.F. et al. *Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes*. Am J Hum Genet 2005, 76(4): 561-71.

24. Cervin, C., Lyssenko, V., Bakhtadze, E. et al. *Genetic similarities between latent autoimmune diabetes in adults, type 1 diabetes, and type 2 diabetes*. Diabetes 2008, 57(5): 1433-7.

25. Tsiavou, A., Hatziagelaki, E., Chaidaroglou, A., Manginas, A., Koniavitou, K., Degiannis, D., Raptis, S.A. *TNF-alpha, TGF-beta1, IL-10, IL-6, gene polymorphisms in latent autoimmune diabetes of adults (LADA) and type 2 diabetes mellitus*. J Clin Immunol 2004, 24(6): 591-9.

26. Kononenko, I.V. *Association of IRS-2 Gly1057Asp and IRS-1 Ala513Pro polymorphism with insulin resistance in patients with latent autoimmune diabetes in adults (LADA).* 42nd Annu Meet Eur Assoc Study Diabetes (EASD) (Sept 14-17, Malmö) 2006, Abst 0296.

27. Liao, L., Zhou, Z., Li, X. et al. *Vitamin D receptor gene polymorphism in Southern Chinese adults with latent autoimmune diabetes (LADA).* 41st Annu Meet Eur Assoc Study Diabetes (EASD) (Sept 12-15, Athens) 2005, Abst 280.

28. Brophy, S., Brunt, H., Davies, H., Mannan, S., Williams, R. *Interventions for latent autoimmune diabetes (LADA) in adults.* Cochrane Database Syst Rev 2007, (3): CD006165.

29. Maruyama, T., Shimada, A., Kanatsuka, A., Kasuga, A., Takei, I., Yokoyama, J., Kobayashi, T. *Multicenter prevention trial of slowly progressive type 1 diabetes with small dose of insulin (the Tokyo study): Preliminary report*. Ann NY Acad Sci 2003, 1005: 362-9.

30. Thunander, M., Thorgeirsson, H., Torn, C., Pettersson, C., Landin-Olsson, M. *Early insulin treatment in latent autoimmune diabetes in adults (LADA) did not improve residual beta cell function or metabolic control*. 44th Annu Meet Eur Assoc Study Diabetes (EASD) (Sept 7-11, Rome) 2008, Abst 972.

31. Brophy, S., Davies, H., Bain, S. et al. *Randomized, controlled, parallel-group prospective study to investigate the clinical*

effectiveness of early insulin treatment in patients with latent autoimmune diabetes in adults. BMC Endocr Disord 2008, 8: 8.

32. Zhou, Z., Li, X., Huang, G., Peng, J., Yang, L., Yan, X., Wang, J. *Rosiglitazone combined with insulin preserves islet beta cell function in adult-onset latent autoimmune diabetes (LADA).* Diabetes Metab Res Rev 2005, 21(2): 203-8.

33. *Efficacy and safety of Diamyd® in patients with LADA (latent autoimmune diabetes in adult) (NCT00456027).* ClinicalTrials.gov Web site, November 13, 2008.

34. Agardh, C.-D., Cilio, C.M., Lethagen, A. et al. *Clinical evidence for safety, efficacy, and immunomodulation by a novel therapeutic intended for treatment of autoimmune diabetes.* 64th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 4-8, Orlando) 2004, Abst 272-OR.

35. Raz, I., Elias, D., Avron, A., Tamir, M., Metzger, M., Cohen, I.R. *Beta-cell function in new-onset type 1 diabetes and immunomodulation with a heat-shock protein peptide (DiaPep277). A randomised, double-blind, phase II trial*. Lancet 2001, 358(9295): 1749-53.

36. *Safety, tolerability, immunological and clinical efficacy of multiple subcutaneous doses of DiaPep277 in latent autoimmune diabetes in adults (LADA) (NCT00058981).* ClinicalTrials.gov Web site, November 13, 2008.