# Latent autoimmune diabetes in adults (LADA)

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**UNIVERSITY OF ZAGREB**
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# Latent autoimmune diabetes in adults (LADA)

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**ABBREVIATIONS**

| | |
|---|---|
| DKA: | Diabetic ketoacidosis |
| DM 1: | Diabetes mellitus type 1 |
| DM 2: | Diabetes mellitus type 2 |
| FPG: | Fasting plasma glucose |
| GADA: | Glutamic acid decarboxylase antibodies |
| GWAS: | Genome-wide association study |
| HbA1C: | Hemoglobin A1C |
| IAA: | Insulin autoantibodies |
| IA-2: | Islet antigen-2 |
| ICA: | Islet cell cytoplasmic autoantibodies |
| LADA: | Latent autoimmune diabetes in adults |
| OGTT | Oral glucose tolerance test |
| PCP: | Plasma C-peptide |
| ROC | Receiver operating characteristic |

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## Abstract

**Latent autoimmune diabetes in adults (LADA)**

**Allan Gutlić**

Latent autoimmune diabetes in adults (LADA) is a form of diabetes with a wide range of phenotypic presentations. This review focuses on the best diagnostic method based on current studies and examines the best treatment approach once diagnosis has been made in patients with LADA. Based on glutamic acid decarboxylase autoantibody (GADA) titers it can be divided into either LADA 1 or LADA 2. The former sharing clinical features of DM 1 with quicker onset of insulin dependence, the latter resembling DM 2 with higher BMI and less need for insulin. The clinical and genetic heterogenuity of LADA has casued much contraversery as it has been debated wether or not it should be considered as a separate entity or part of a continuum between DM 1 and DM 2. However, proper diagnosis and treatment is highly needed for this subgroup of patients, as they eventually have worse metabolic control and are more prone to DKA than DM 2 patients. The proportion of patients with LADA and DM 1 is roughly estimated to be equal considering the fact that about 10 % of DM 2 patients actually belong to the LADA subgroup. With regards to this large number of LADA patients, screening methods are crucial for indentification, correct treatment and stricter metabolic control.



**Keywords:** LADA, autoimmune, diabetes, GADA, diagnostic criteria

## Sažetak

**Latentni autoimunosni dijabetes odraslih**
**Allan Gutlić**

Latentni autoimunosni dijabetes odraslih (LADA - akronim po engleskom nazivu) je oblik šećerne bolesti širokog spektra fenotipa. Ovaj prikaz je usredotočen na metode dijagnoze temeljene na ispitivanjim i na terapijski prostup kada se dijagnoza postavi. Temeljem titra antitijela na dekarboksilazu glutaminske kiseline (GADA) može se podijeliti u LADA 1 i LADA 2. LADA 1 je sličan tipu 1 šećerne bolesti, s bržim nastankom ovisnosti o inzulinu dok LADA 2 klinički više liči na tip 2, uz veći indeks tjelsne mase i s manjom potrebom za inzulinom. Klinička i genetska hetergenost LADA izaziva dosta kontroverzi. Raspravlja se jesu li to različiti entiteti ili se radi o kontinuumu između tipa 1 i tpa 2 šećerne bolesti. U svakom slučaju, prava dijagnoza je nužna za ovu skupinu bolesnika jer oni postaju metabolički loše regulirani i skloniji su ketocidozi od onih s tipom 2 bolesti. Udio bolesnika s LADA i tipom 1 se cijeni ugrubo istim zbog činjenice da je oko 10 % osoba s tipom 2 šećerne bolesti u ovoj podskupini. Obzirom na velik broj osoba s LADA dijagnostičke metode su bitne za njihovu identifikaciju koja omogučuje prikladnije liječenje i striktniju metaboličku kontrolu.



**Ključne riječi:** LADA, autoimunost, šećerna bolest, GADA, dijagnostički kriteriji

## Introduction

The two main types of Diabetes are type 1 and type 2 diabets. The incidence of DM 1 is higher in children 5-7 years of age and around puberty (1). DM 1 patients often are leaner with insulin dependence, have lower C-peptide levels and are more prone to developing ketoacidosis at first time diagnosis (2). Out of the two main types, DM 2 is by far the more prevalent one. It is now the fastest growing type and thus creating an even higher health burden globally, especially in developed countries but also in developing countries (3). Some potential reasons for this rapid growth is a general increase in life expectancy, improved diagnosis and faulty dietary habits with lack of exercise (4). LADA as an indistinctly described entity lies somewhere in between type 1 and 2 diabetes and has been called 1.5 diabetes. It shares a common genetic, immunologic and clinical characteristics with both types. This wide continuum of LADA represents a challenge in the diagnosis and treatment approach. There is a necessity to better define LADA and formulate a treatment approach. It could play a key role in slowing progression and improve prognosis in these patients.

LADA is clinically more similar to type 2 diabetes but have some genetic characterisics in common with type 1 diabetes. Therefore it is often underdiagnosed and instead treated as type 2 diabetes. No clear data can be found on the global prevalence of LADA but an estimation based on several studies from Europe and Asia indicate that 3-14% of patients with DM 2 have autoantibodies and hence should be classified as LADA (5). Glutamic acid decarboxylase autoantibody (GADA) positive DM 2 patients seemed to be more frequent in northern Europe than southern Europe and Asia but due to the lack of clear diagnostic criteria this difference could be attributed to selection bias and variations in methods for diagnosis. The criteria for LADA are not strictly set and current standard diagnostic criteria do not exist. The three criteria proposed by the immunology of diabetes society are as follows:

1. Presence of autoantibodies in plasma.
2. Insulin independence for at least 6 months after diagnosis
3. An onset of disease after 30 years of age.

The second criteria above distinguishes LADA from DM 1. This criteria is dependent on which stage of disease the patient is diagnosed at and when the physician decides

to initiate insulin therapy making it subjective. The accuracy of the age cut off in the third criteria is also questionable becasue autoantibody status in a study with DM 2 children was similar in frequency compared to DM 1 children (6).

By implementing these criterias in all studies, comparisons can be made with more certainty. The heterogeneity of diabetes still poses a problem for classification of LADA since not all subgroups of patients might express the same phenotype according to antibody postivity.

## Genetic similarities

The role of genetics in diabetes is a perplexing issue invloving genetic and environmental factors. External environmental influences can affect incidence rates because differences are seen in rates among countries. Higher rates are observed in monozygotic twins compared to dizygotic confirming that internal genetics are partially responsible for disease development. The complex interaction of these two factors have made it difficult to establish exact predictors and mechanisms leading to acquisition of the disease. Many genes have been discovered for DM 1, while those for DM 2 have initially been harder to find. Recent advances in genotyping by GWAS have gain more insight on the genes associated with DM 2. Unfortunatley the interest in finding specfic genes for LADA is low and no single genes exist that are found only in LADA. Instead an admixture of genes from both DM 1 and DM 2 is seen. To understand the genetic composition of LADA we must first separately consider the genes responsible for DM 1 and DM 2 respectively.

The major high risk genes involved in pathogenesis of DM 1 have been known for a longer time and they are found on HLA class II. They are all HLA-DR/HLA-DQ haplotypes, namely DRB1, DQA1 and DQB1. The two combinations of alleles that confers the greatest risk for DM 1 are called DR3 and DR4. Being heterozygos for these two alleles contributes to the highest risk of acquring DM 1 (7). The HLA locus is generally thought to be responsible for approximately 50 % of genetic causes for developing DM 1. The number of studies on LADA and the genetic correlation to DM

1 are few but the HLA II class is implicated to play a role in LADA as well (8-10). Another locus that attributes to risk in both phenotypes is the INS locus (11, 12).

A large number of new genes associated with DM 2 have recently been found with the help of GWAS. The most important of these with the greatest impact in DM2 pathophysiology is a transcription factor called TCF7L2, a member of the Wnt signaling pathway (13). A global meta-analysis investigating the association of DM 2 and TCF7L2 showed a pooled odds ratio of 1.46 (CI, 1.42-1.51) in patients versus controls. Overexpression of TCF7L2 in islet cells is seen in DM 2 and is linked to diminished insulin secretion (14). The impact of TCF7L2 has been shown to be of equal significance in LADA (15). Though the impact in LADA seem to be higher in patients that have a lower BMI (16). Patients with low GADA titers are more prone to have a DM 2 phenotype (LADA 2) and as expected the frequency of TCF7L2 is higher in this subgroup of patients (17).

## Clinical features

Newly diagnosed type 1 diabetics are usually have a lower BMI and systolic blood pressure than type 2 diabetics (18). Due to minimal or absent insulin secretion type 2 diabetics are more prone to present with diabetic ketoacidosis. The lack of insulin forces the body to break down fatty acids through beta oxidation instead of glucose thus creating ketones in the process. LADA falls somewhere in between these two, with the presentation depending on autoantibody status, especially the presence of glutamic acid decaboxylase antibodies (GADA). A study on the effect of GADA titers in LADA patients was done and three groups of patients were compared (19). Those with high titers (>17.2U/mmol), low titers (>1U/mmol and <17.2Ummol) and a GADA negative group of type 2 diabetics. There was a lower incidence of high BMI, hypertension, high LDL and low HDL in the group with high GADA titers than in the other two groups which had similar results (19). These differences in clinical profile between LADA with high and low GADA titers has led them to be sub-classified as LADA 1 and LADA 2 respectively. Zampetti et al. looked at the concomitant probability of other autoimmune diseases comparing the same three groups but with

different cut-off values for high and low GADA titers. They found a significantly increasing trend of thyroid autoimmunity in both men and women in the high GADA titer group (20). The odds ratio for males when comparing the high titer group with the T2DM group was 8.9 CI (4,1-19.3) and females 3.6(1.8-6.8).

## Diagnosis and screening

According to WHO diabetes can be diagnosed by having symptoms of diabetes (polyphagia, polyuria, polydipsia and weight loss) and a fasting plasma glucose (FPG) of ≥7.0mmol/l, a random venous glucose of ≥11.1mmol/l or a plasma glucose of ≥11.1mmol/l 2 hours after ingesting 75mg anhydrous glucose in an oral glucose tolerance test (OGTT) (21). With the lack of diabetic sympotms it is essential to perform a second confirmatory glucose test. Until recently the recommendation was to refrain from using Hemoglobin A1C (HbA1C) in diagnosis but WHO have in 2011 accepted the use of it as well. A HbA1C of ≥48mmol/l (6.5%) is positive and reflects the glucose status in the body the last three months. There are no clear diagnostic criteria for LADA since it is a widely heterogenous disease entity. There is a need for clinical diagnostic guidlines to correctly diagnose and treat LADA patients because of the current lack of awareness among physicians leading to patients not being treated optimally. As mentioned earlier not all LADA patients progress to insulin deficiency at the same rate. They can either be LADA 1 or 2 and their progression can be predicted by autoantobodies (especially GADA) and monitored with C-peptide levels. Screening for autoantibodies in non-insulindependent adults can be rather costly if done on every single patient. To avoid screening all type two diabetics with GADA it is better to classify them according to probablility of having LADA before performing antibody testing. Currently it is common to screen suspected LADA patients for autoantibodies solely based on a BMI≤25. Given the increasing prevalence of obesity in general it is now even less accurate to use only BMI when deciding if autoantibody screening is necessary. Therefore five clinical screening criterias have been set by Fourlanos et al (22). The five criteria focus on an age of onset < 50 years, BMI≤25, acute symptoms of diabetes, personal history of DR3/DR4 associated autoimmune disease and family history of DR3/DR4 associated autoimmune disease. For diabetic

patients with 2≥ criteria, the sensitivity of having LADA was 90% and specificity 71%. The negative predictive value was 99% for a score that was 1≤, thus making this screening method useful in excluding LADA patients. When creating these criteria the patients included were 30-75 years old. LADA was defined in the same way as described earlier by the immunology of diabetes society with an exception that only GADA was used for autoantibody status.

To better illustrate this complete diagnostic process, a diagnostic flowchart was made and is presented in figure 1. The flowchart shows that patients with 2≥ criteria can be screened for low or high GADA titers and divided into the subgroups LADA 1, LADA 2 or DM 2. The cut off value for a postive titer was ≥20U/ml and the cut off value chosen for the higher titer was ≥175U/ml. Type 2 diabetics had titers below 20U/ml.

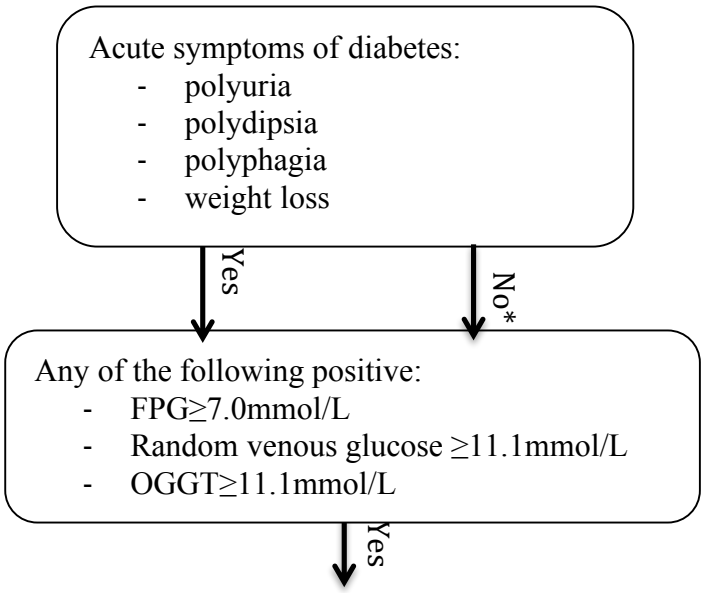
There is an ongoing debate regarding which cut off values to use to differentiate between the LADA subtypes. The difference in treatment approach should guide this division of LADA and the two main points in the treatment considerations are the rate of insulin deficiency and the degree of insulin resistance. In a study a receiver operating characteristic (ROC) curve was used to decide on which GADA titer should be used as a cut off value to best categorize LADA into its two subtypes (23). The most distinct difference in rate of insulin deficiency and degree of insulin resistance was observed at a titer of 175U/ml with a sensitivity of 54.5% and a specificity of 92.1%. Other studies have also used cut off values in the same range of 175-180U/ml (23, 24).

GADA has proven to be the best and most sensitive autoantibody to diagnose LADA in several studies and therefore the most appropriate to screen for (25, 26). Antibody assays should be performed in a standardized manner with the a set specificity and sensitivity as suggested by the diabetes antibody standardization program. Many authors found that screening for multiple antibodies and not only GADA increases the diagnostic accuracy and better predicts the risk of progression to insulin dependence (27-29). It has been shown that the postivity of GADA and islet cell cytoplasmic autoantibodies (ICA) together yield a higher positive predicitve value of requiring insulin at an earlier rate compared to GADA alone, this being even more evident in

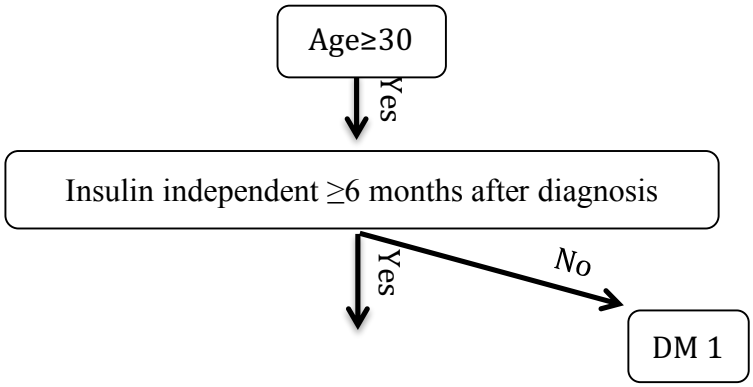
patients >45 years of age (25, 30). These results also comply with other studies in which patients with positivity of both ICA and GADA displayed a LADA 1 phenotype with faster beta cell function decline (31, 32). Single GADA postivity in high titers also displayed the LADA 1 phenotype but not single ICA positivity(29, 32). Patients with high titers of GADA more frequently had other autoantibodies positive as well (20). Therefore it could be satisfactory to use high GADA titers as a diagnostic marker for LADA in young patients that fulfill the other criteria presented in the flowchart shown in figure 1. For patients older than 50 years of age it could worth to perform additional antibody testing for ICA antibodies for a more accurate diagnosis. The presence of islet antigen-2 (IA-2) autoantibodies were highly predicitve of future insulin dependence but were expressed only in a few patients (26, 33). C-peptide is endogenously released with insulin and functions as marker of beta cell function and can now be more cheaply measured in urine samples (34). C-peptide levels are now mostly used to differentiate between type 1 and 2 diabetes but it could function as a screening tool for LADA (35).

***Diagnostic flowchart***

**WHO criteria**




**LADA clinically according to Immunology of diabetes society**




**Screening for LADA according to Fourlanos et al.**

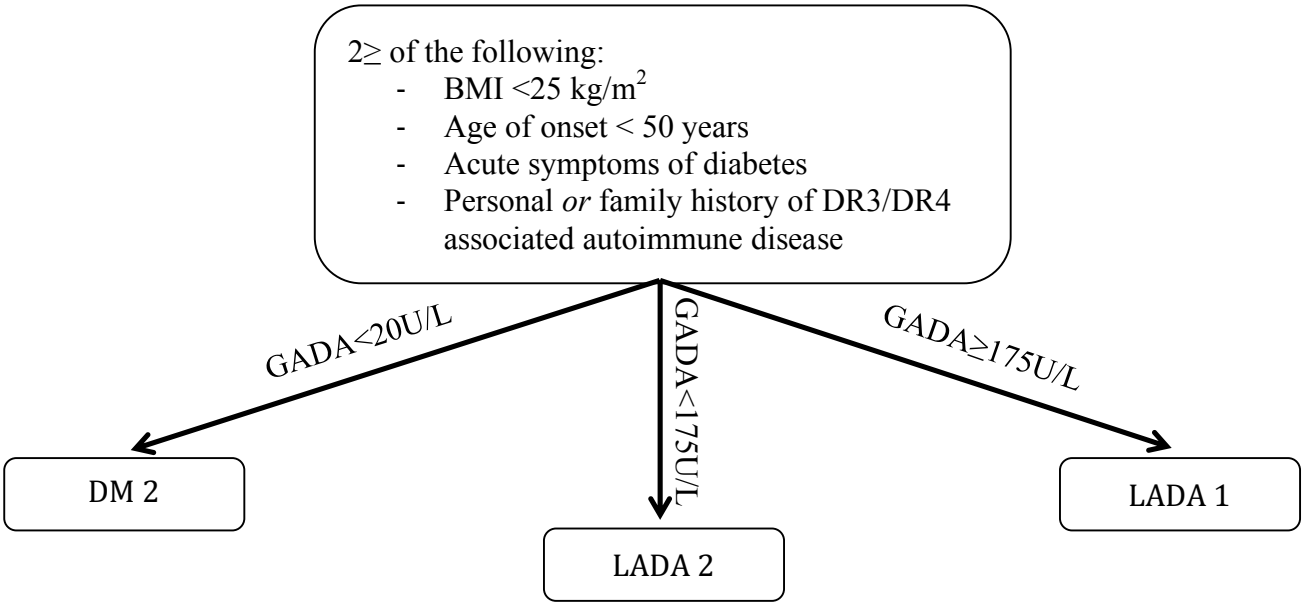



Figure 1.
*Second confirmatory (OGTT, FPG)

# Treatment strategies

## Insulin

The slower onset of LADA to insulin deficiency opens up for an opportunity of a better planned treatment strategy. Insulin will eventually be necessary when the beta cell function dissapears in LADA. It has been hypothesized if early insulin treatment in the early stages could be helpful in slowing the progression to insulin deficiency. Early adminstration of exogenous insulin is thought to decrease the stress on the beta cells and thus perserving their secretory capacity. More active secretion of endogenous insulin also increases the body's autoimmune response with beta cell damage as a consequence(36). Experimental diabetic non obese diabetic (NOD) mice had less amount of macrophage infiltrates in the exocrine pancreas if they were prophylactically treated with insulin compared to the non treated control (37). Exogenous insulin can promote acivation of T regs which have anti-inflammatory properties and can even induce remssion of the disease, discussed more in detail later in the review (38). In the diabetes prevention type 1 study, patients with first or second degree relatives with DM 1 were selected to estimate if oral insulin adminstration can be used in preventing the devlopment of DM 1 (39). In this randomized double blind placebo control study 372 patients, positive for islet cell antibodies, were split in equal sizes and either assigned to a treatment group that received 7.5mg/day of oral insulin or placebo. Median follow-up time was 4.3 years at which 43 patients in the treatment arm and 53 patients in the placebo arm had developed diabetes. The yearly incidence rates of diabetes were similar in both groups and oral insulin did not help in slowing down or preventing diabetes. A subgroup of treated patients with high titers of insulin autoantibodies (IAA) did have a delayed onset of diabetes but this relationship remains unclear since they generally had a slower onset compared to lower titer groups. The practical limitation of not being able to use subcutaneous insulin in these patients that still have not developed diabetes might affect the study outcome and questions the validity of this study. Oral insulin is partly destroyed by gastric acid and the full amount will not reach the intestines. The

main problems are a low bioavailbility and patient variation in pharmacodynamics (40). Other researchers have found that small doses of subcutaneous insulin can prevent and delay the progression to insulin dependence in LADA patients with high GADA titers and a preserved beta cell function at the beginning of the intervention (41, 42). Therefore benefits of using early insulin in a preventive manner might depend on route, timing and autoantibody status of LADA patients. If deciding on early intervention these factors should be considered. A swedish prospective study on LADA patients examined the effects of early insulin vs conventional treatment (43). They noticed a significantly better metabolic control, lower HbA1c and no difference in C-peptide levels in those treated with insulin.

The studies done until now on early insulin in LADA and benefits in preserving beta cell function still show discrepancies and larger scale studies are essential to clarify the uncertainties.

## Oral hypoglycemics agents

In the previously discussed studies, early insulin in High GADA titer patients could slow the progression to insulin dependence and improve metabolic control when compared to sulfonylurea treatment (41, 42). Similar conclusions regarding metablic control was observed by Cabrera-Rode et al. when using insulin as a monotherapy and not in combination with glibenclamide (44). In this study all the patients were intially ICA positive and after 1 year follow-up all the patients assigned to insulin monotherapy became ICA negative, in contrast to patients receiving combination therapy where all patients remained positive.

Thiazolidinediones are suggested to decrease the destructive autoimmune inflammatory effects of T-cells on beta cells through activation of PPAR-γ receptors present on T-cells (45, 46). Ciglitazone a PPAR-γ-ligand have been show to increase the effect of T regs (47). A pilot study compared insulin treatment alone to insulin and rosiglitazone (48). They measured C-peptide levels 2h after a 75mg glucose meal

(PCP) every six months and at 12 and 18 months PCP remained stable in the combination group while decreasing in the insulin monotherapy group. This relationship was confirmed in a larger study where GADA levels were taken into account (49). Patients with GADA titers >175U/ml were again given insulin-only or insulin and rosiglitazone treatment. The C-peptide levels were significantly higher in the group with combination therapy after two years of follow-up but the gap diminshed and the difference became insignifiacnt after three years. There are proven adverse cardiovascluar effects from rosiglitazone and it has been taken off market in several countries.

A more popular group of drugs are the DPP-4 inhibtors. The fact that they rarely cause hypoglycemia and generally have a better side-effect profile than sulfonylureas has lead to an increased interest on their effect on LADA as well. In a open-labeled randomized control trial patients recently diagnosed with LADA were followed for a year. They either received insulin as monotherapy or in combination with 100mg/day sitagliptin (50). Compared to baseline, the C-peptide levels decreased significantly in the group treated only with insulin but remained steady in the patients additionally given sitagliptan. A post hoc study and a randomized double blind control study confirmed this beneficial effect off DDP-4 inhibitors on C-peptide levels (51, 52). In the former study patients were given saxagliptin or placebo and those on treatment had better sustained beta cell function 24 weeks after baseline. The same trend was observed in the two year double blind RTC were patients where given linagliptin or glimepiride. The mechanism of DPP-4 inhbitors on perservation of beta cell function in humans is still uncertain. Nonobese diabetic mice treated with DPP-4 inhibitors have shown reversal of their recent onset diabets through stimulation of beta cell replication and increase in T regs (53). Larger prospective studies are still necessary to uncover possible mechanisms in humans and to further explore the certainty of the benficial effects on beta cell preservation.

## The role of regulatory T-cells (T regs)

The immune supressor cells called T regs are important in the development of peripheral tolerance in diabetes. They are derived from the thymus and are the body's natural defence against autoimmunity. A transcription factor called Foxp3 is expressed by T regs and this factor plays an important role in their development (54). The identification of T regs involves their expression of Foxp3. Decrease levels of T regs have been seen in mice with type 1 diabetes due to dysfunction of Foxp3. The same effect of low number T regs on development of autoimmune diabetes in humans have proven to be false in two studies (55, 56) but true in one study which showed decreased number of CD4+ T-cells with intermediate levels of CD 25 in early diagnosed LADA patients compared to healthy controls (57). Similar levels of T regs was measured for type 1 diabetics and in controls. The function could be more important than the number of T-regs in maintaining autoimmune tolerance (55). Both stable and instable T regs have been described (54). The goal of future and present therapy is to achieve enough functionally stable T regs and this can be done by adding ex-vivo expanded autologous polyclonal Tregs or converting the already instable cells into stable (54, 58). T regs instability can be caused by less response to certain cytokines due to decreased receptor affinities. GITR also a marker associated with T regs and its deficit implicated in their instability and poorer chance of survival (59). Instable T regs secrete lower amounts of anti-inflammatory cytokines (IL-35 and IL-10) and their effector function potentiates. Epigentic changes in the Foxp3 region through demethylation can lead to instabiliy (54). Marek Trzonkowska et al. studied 12 children diagnosed with T1D within 2 months and followed them for one year after they received autologous polyclonal T regs (60). They were compared at 4 and 12 months to 10 controls matched for sex, age and duration of the disease. Half of the 12 patients in the treatment arm received two doses of T regs and the rest one dose. Less insulin dependence, lower HbA1c and higer fasting C-peptide levels was seen in treatment vs control group at 4 and 12 months. The C-peptide levels were even higher for the patients treated with two doses compared to those treated with one dose. Eight of 12 patients in the treatment group had remission of their diabetes vs none in the control group. Unfortunately readministration with a subsequent dose had a decreased effect and the positive protective effects wore of eventually as the concentrations of T

regs in plasma decreased. Generally there were no serious adverse effect in the treament arm. Another similar study on T1D adults with less promising resluts was performed by Bluestone et al. in a phase 1 trial. They investigated the effect and safety of adding autologous ex-vivo expanded Tregs in 14 recently diagnosed adult T1D patients (61). The patients were divided in 4 cohort groups with a follow-up time of 104-182 weeks between the groups. A decrease of >50% in C-peptide levels occured in two of the cohorts after 78 weeks but remained the same in the other two cohorts even after 2 years. Upon completion there was no infusion reactions or other serious adverse effects short-term, proving the safety of this approach and encouraging a phase 2 trial with increased number of patients to get more reliable results.

A possible reason for the added T regs not providing the full effect in the adult patients the start of treatment was done several weeks post-diagnosis for them and within two weeks for the children. Marek Trzonkowska et al. stated that higher intial C-peptide was correlated with a longer remission time. Pharmacotherapy with CD3 monoclonal antibodies in some studies have maintained C-peptide levels in recent onset DM 1 patients treated with them (62-64). CD3 antibodies have a potential to restore stability in T regs that are unstable and promote an increase number of normal T regs (65).

## Discussion

The current knowledge about LADA is still lacking with no clear treatment guidelines. There is a need for standardization of LADA to enable proper analysis of data and better comparison of results between studies. The heterogenous nature of this disease has prevented the realization of this even though LADA has by many been recognized as seperate type of diabetes for some time now. Others still consider LADA as a part of a spectrum from DM 1 to DM 2 with LADA 1 and LADA 2 in between. This assumption could lead to less research being done on LADA and in turn negatively affect this group of patients. Incorrect treatment of LADA patients with hypoglycemics as they were type 2 diabetics can lead to long term complications. They are more often in need of stricter disease surveillance to maintain proper metabolic control and more often present with other concomitant autoimmune

diseases. This group should be treated with insulin earlier to achieve better glycemic control and less beta cell failure. The timing of insulin and gliptin treatments could be crucial for perserving beta cell function for as long as possible. More and larger long term prospective studies are needed to validate the results in the smaller studies with short follow-up time. The studies examined in this review contain a lot of systematic errors and the analyses compared are not done with identical methods and criterias. The difference in LADA between various ethnicities need to be further elucidated as well. High GADA postivity seem to be a constant predictor of LADA regardless of ethnicity (27, 66), but response to various treatments might differ. DPP-4 inhibtors and acarbose have proven more efficacious in asian population than in caucasian (67, 68). If this is related to ethnicity, environmental exposures in each geographic area or a combination of both remains unknown.

## Conclusion

Currently, without a clear marker of exact diabetes classification in slowly progressive autoimmune diabetes in adults, the best that can be done for recently diagnosed patients is to carefully evaluate their diabetes subtype in a meticulous manner so that the right therapeutic approach can be chosen. Improper glucose control in incorrectly diagnosed DM 2 patients can eventually lead to long term complications.

For LADA patients with high GADA titers and preserved beta cell function at diagnosis, early insulin treatment might prevent further beta cell detoriation. Sulfonylureas have an adverse effect on C-peptide levels, while DPP-4 inhibitors have been shown to sustain them and are thus recommended. Immunotherapy with autologous polyclonal Tregs and CD3 antbodies have both shown promising results regarding C-peptide levels although the studies conducted have been small with few participants.

The need for studies of larger scale is essential to develop better defined criteria, guidelines and treatment approaches in this group of underdiagnosed patients. The present research implicates that these issues should not be neglected.

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## Biography

Allan Gutlić was from an early age influenced by the medical profession at home. During his teenage years he was competing in swimming on a national level. Unfortunately due to lack of time he later on quit swimming in his early high school years in order to focus on his academic career. He started his academic studies in Malmö, Sweden, where he enrolled into a science oriented high school. It was not until then his interest for medicine grew and he decided to apply for the medicine program in Zagreb medical university.