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ARTICLE

Worse glycaemic control in LADA patients than in those with type 2 diabetes, despite a longer time on insulin therapy

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Abstract
Aims/hypothesis Our aim was to study whether glycaemic control differs between individuals with latent autoimmune diabetes in adults (LADA) and patients with type 2 diabetes, and whether it is influenced by time on insulin therapy.
Methods We performed a retrospective study of 372 patients with LADA (205 men and 167 women; median age 54 years, range 35–80 years) from Swedish cohorts from Skåne (n= 272) and Västerbotten (n=100). Age- and sex-matched patients with type 2 diabetes were included as controls. Data on the use of oral hypoglycaemic agents (OHAs), insulin and insulin–OHA combination therapy was retrieved from the medical records. Poor glycaemic control was defined as HbA_{1c} ≥7.0% (≥53 mmol/mol) at follow-up.
Results The individuals with LADA and with type 2 diabetes were followed for an average of 107 months. LADA patients were leaner than type 2 diabetes patients at diagnosis (BMI 27.7 vs 31.0 kg/m^2; p<0.001) and follow-up (BMI 27.9 vs 30.2 kg/m^2; p<0.001). Patients with LADA had been treated with insulin for longer than those with type 2 diabetes (53.3 vs 28.8 months; p<0.001). There was no significant difference between the patient groups with regard to poor glycaemic control at diagnosis, but more patients with LADA (67.8%) than type 2 diabetes patients (53.0%; p<0.001) had poor glycaemic control at follow-up. Patients with LADA had worse glycaemic control at follow-up compared with participants with type 2 diabetes (OR= 1.8, 95% CI 1.2, 2.7), adjusted for age at diagnosis, HbA_{1c}, BMI at diagnosis, follow-up time and duration of insulin treatment.
Conclusions/interpretation Individuals with LADA have worse glycaemic control than patients with type 2 diabetes despite a longer time on insulin therapy.

Keywords GAD isoform 65 · HbA_{1c} · Latent autoimmune diabetes in adults

Abbreviations

GAD65A	GAD isoform 65
IQR	Interquartile range
LADA	Latent autoimmune diabetes in adults
OHA	Oral hypoglycaemic agents
RU	Relative unit
VIP	Västerbotten Intervention Program

Introduction

Latent autoimmune diabetes in adults (LADA) is an autoimmune form of diabetes in which patients may produce autoantibodies against GAD isoform 65 (GAD65A) [1]. Approximately 5–10% of patients who are initially diagnosed with type 2 diabetes by clinicians in fact have LADA

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[2]. LADA is a heterogeneous group of diseases that share biochemical, genetic and phenotypic characteristics with both type 1 and type 2 diabetes [2, 3].

There is no consensus regarding the optimal treatment for patients with LADA. It has been suggested that treatment should start with insulin since LADA is a form of type 1 diabetes and the majority of patients will eventually become insulin-dependent [4, 5]. Two small studies have shown beneficial effects of early insulin therapy in patients with LADA [6, 7]. In the UK Prospective Diabetes Study, however, initiation of insulin or oral hypoglycaemic agents (OHAs) did not influence glycaemic control in individuals with LADA [2].

The aim of the current retrospective study was to evaluate whether glycaemic control differs between patients with LADA and those type 2 diabetes, and whether it is influenced by time on insulin.

Methods

Design and population

In this observational retrospective study, we identified patients with LADA and with type 2 diabetes in Skåne and Västerbotten, two counties in Sweden. Controls (patients with type 2 diabetes) were matched (1:1) for sex, age at diagnosis (±3 years) and year of diagnosis (±1 year). The Skåne cohort was also matched for ethnicity as 22% of patients had non-Swedish backgrounds (northern and central Europe, the Balkans or the Middle East). There was no matching for ethnicity in the Västerbotten cohort because less than 4% of the patients had ethnic backgrounds other than Swedish. The participants gave their informed consent to participate in the registers, and the study was approved by the ethics committee at Umeå University, Umeå, Sweden.

The follow-up was conducted in Skåne and Västerbotten using the same protocol. All Swedish citizens have a unique social security number by which they can be traced in national databases even if they have moved out of the county, emigrated or died. Thus, only 11 and eight individuals from the Skåne and the Västerbotten cohorts, respectively, could not be followed up. The follow-up time did not differ between those with LADA and those with type 2 diabetes, but patients in Västerbotten were followed for a longer time than patients in Skåne (Table 1).

The Skåne cohort Patients were diagnosed between 1989 and 2007 and were participants in the Diabetes Registry of Southern Sweden (Diabetes 2000). The follow-up period ran from 1996 to 2009. By 2009, the database included 7,432 patients. Information on age, sex, GAD65A levels, HbA_{1c} values at diagnosis of diabetes, type of diabetes, year of diagnosis and BMI were retrieved from the database. Information on GAD65A and C-peptide levels was available to clinicians at the time of diagnosis. The Skåne cohort also included data on HbA_{1c} values 6 months and 3 and 5 years after diagnosis, as well as C-peptide and fasting glucose levels. Information on diabetes therapy was obtained from the medical records of the Department of Endocrinology in Malmö and from primary healthcare centres in Skåne.

The Västerbotten cohort Since 1986, all inhabitants of Västerbotten County have, as part of the Västerbotten Intervention Program (VIP), been invited for health examinations during the years they turn 40, 50 and 60. They have also been asked to donate a blood sample for medical research [8].

In 2002, the VIP database was linked to the patient registries for both primary healthcare and hospitals in Västerbotten. Out of 67,000 participants in the VIP, 1,948 were diagnosed with diabetes between 1972 and 2004 and were followed up from 1995 to 2008. Data collection took place in 2007–2008. A questionnaire containing information about the diabetes registry was sent out, and 1,661 of the patients (85%) consented to participate. These patients constitute the DiabNorth register [9].

Specially trained nurses reviewed the patients' medical records, filled in a validation form and collected information on blood glucose, HbA_{1c} level at diagnosis, BMI, presence of diabetes symptoms at diagnosis, type of diabetes, year of diagnosis and type of diabetes treatment. Of the 1,661 patients, 1,267 (76%) had been diagnosed with type 2 diabetes by their physicians. Blood samples were analysed for the presence of GAD65A. Specialists in diabetology reclassified the patients after analysis of GAD65A. Patients diagnosed with secondary diabetes due, for example, to cancer or medication affecting glucose control were excluded from the study.

Additional data collection

Data on diabetes therapy were collected from medical records for both cohorts. Therapy was categorised as diet and exercise recommendations, OHAs, insulin or OHA plus insulin. The time in months spent on each treatment was calculated. Time on OHA or insulin was defined as the time from the first prescription until the end of follow-up or termination of treatment. For patients who took insulin during two or more periods of their disease, the sum of these periods was calculated and considered to be the total time on insulin treatment.

Definitions

Diabetes was defined according to WHO criteria [10]. The following modified version of the Immunology of Diabetes Society definition was used as the definition of LADA [11]: (1) age 35 years or older at onset of diabetes, (2) the

Table 1 Characteristics of patients with LADA and type 2 diabetes in the Skåne and Västerbotten cohorts

Characteristic	Total			Skåne			Västerbotten			Skåne/Västerbotten	
Number	LADA 372	T2D 372	*p* value	LADA 272	T2D 272	*p* value	LADA 100	T2D 100	*p* value	LADA/LADA *p* value	T2D/T2D *p* value
At diagnosis											
Age (years)	54.5 (10.8)	54.5 (10.8)	0.96	54.4 (11.8)	54.4 (11.8)	1.0	54.9 (7.3)	54.8 (7.4)	0.93	0.62	0.75
Male (%)	55.1	55.1		54.8	54.8		56.0	56.0			
BMI (kg/m^2)	27.7 (5.9)	31.0 (5.5)	<0.001	27.3 (6.1)	31.2 (5.8)	<0.001	28.8 (5.2)	30.6 (4.8)	0.012	0.05	0.35
HbA_{1c} (%)	8.9 (2.5)	8.6 (2.5)	0.19	8.9 (2.4)	8.6 (2.3)	0.14	8.8 (2.6)	8.7 (2.9)	0.79	0.66	0.72
HbA_{1c} (mmol/mol)	73.6 (27.6)	70.9 (27.6)		74.3 (26.9)	70.5 (25.4)		72.1 (29.2)	71.7 (31.5)			
GAD65 (IU/ml)							139 (202)	10.7 (4.7)	<0.001		
C-peptide (nmol/l)				0.76 (0.59)	1.2 (0.75)	<0.001					
At follow-up											
BMI (kg/m^2)	27.9 (5.5)	30.2 (5.1)	<0.001	27.8 (5.7)	30.7 (5.5)	<0.001	28.1 (4.8)	29.2 (4.0)	0.093	0.66	0.01
HbA_{1c} (%)	7.8 (1.5)	7.4 (1.4)	<0.001	7.9 (1.6)	7.4 (1.4)	<0.001	7.5 (1.3)	7.3 (1.4)	0.23	0.02	0.54
HbA_{1c} (mmol/mol)	62.2 (16.5)	57.3 (15.5)		63.3 (17.1)	57.6 (15.5)		59.0 (14.2)	56.4 (15.3)			
$HbA_{1c} \geq 7$ (%)	67.8	53.0	<0.001	68.0	53.2	<0.001	67.0	52.6	0.04		
Follow-up time (months)	107 (60.6)	107 (63.3)	0.97	94.7 (52.3)	95.5 (54.8)	0.88	137 (69)	135 (73)	0.82	<0.001	<0.001
Duration of treatment regimen (months)											
Diet/exercise	17.9 (30.7)	28.5 (36.5)	<0.001	14.3 (26.3)	26.1 (32.6)	<0.001	27.0 (38)	34.0 (44)	0.23	0.003	0.071
OHA	32.3 (37.6)	49.0 (42.6)	<0.001	27.8 (33.7)	45.2 (42.1)	<0.001	43.5 (44)	58 (43)	0.022	0.002	0.014
Insulin	46.0 (60.9)	14.3 (35.8)	<0.001	44.2 (55.1)	10.3 (26.7)	<0.001	50.5 (73.6)	24.1 (50.5)	0.004	0.43	0.011
Combination	9.1 (24.4)	15.3 (33.7)	0.01	6.4 (17.9)	13.5 (30.4)	<0.001	15.8 (35.1)	19.7 (40.4)	0.47	0.01	0.18
Total insulin	53.3 (62.4)	28.8 (47.2)	<0.001	48.8 (54.4)	23.1 (38.9)	<0.001	65.1 (78.0)	42.5 (61.0)	0.02	0.06	0.01
Duration of treatment regimen (%)											
Diet/exercise				19.4	31.9		22.1	29.1		0.47	0.51
OHA				33.4	48.5		36.9	46.1		0.43	0.61
Insulin				40.2	9.8		31.4	14.1		0.08	0.18
Combination				6.6	11.1		10.3	12.3		0.13	0.65
TIS (months)	23 (39.4)	67 (51.1)	<0.001	21.0 (37.0)	65 (43.0)	<0.001	25.0 (45.5)	71.5 (63.3)	0.003	0.18	0.18

Data are means±SDs, except for TIS and GAD65A, which show median (IQR)

Missing values: HbA_{1c} at diagnosis, 25%; BMI at diagnosis, 18%; BMI at follow-up, 21%

T2D, type 2 diabetes; combination, combination treatment (insulin+OHA); TIS, time to initiation of insulin treatment

presence of circulating islet autoantibodies, and (3) no signs or symptoms of classic type 1 diabetes. In addition, none of the individuals with LADA had ketonuria [12]. Time on insulin was defined as time on insulin alone or in combination with an OHA.

Outcome measures

The main outcome measure was glycaemic control. Poor control was defined as HbA_{1c} ≥7.0% (≥53 mmol/mol) at follow-up as recommended by the recently published position statement of the American Diabetes Association and the European Association for the Study of Diabetes [13]. We studied how glycaemic control was influenced by time on insulin therapy in both patients with LADA and patients with type 2 diabetes.

Laboratory analysis

The Skåne cohort GAD65A levels were measured at the clinical chemistry laboratory by radiobinding assay, performed using ^{35}S-labelled recombinant human GAD65. In the Skåne cohort, GAD65A levels were expressed as relative units (RUs) until the year 2000 and as international units per millilitre (IU/ml) after the introduction of the WHO International Standard [14]. RU=(cpm for sample−mean cpm of three negative controls)/(cpm for a positive internal reference−mean cpm of three negative controls)×100. GAD65A concentrations exceeding 5 RU or 32 IU/ml (the mean+3SD of 296 healthy controls) were considered positive. GAD65A results, expressed as RU or IU/ml, showed a linear correlation up to a concentration of 250 IU/ml [15].

In contrast to many other countries, Sweden uses the Mono S method (Amersham Pharmacia Biotech, Uppsala, Sweden) for HbA_{1c} analysis. Thus, HbA_{1c} values were converted to DCCT standard values using the formula: $HbA_{1c}(\text{DCCT}) = 0.923 \times HbA_{1c}(\text{Mono S}) + 1.345$. Values are presented both in DCCT (%) and International Federation of Clinical Chemistry and Laboratory Medicine (mmol/mol) units. Conversion between DCCT and International Federation of Clinical Chemistry and Laboratory Medicine units was carried out using the following equation: $HbA_{1c}(\text{mmol/mol}) = [HbA_{1c}(\%) - 2.15] \times 10.929$.

Fasting plasma C-peptide levels were measured in duplicate by radioimmunoassay (Peninsula Laboratories, Belmont, CA, USA) [14]. The detection limit was 0.1 nmol/l, and all values below this limit were considered to be 0.01 nmol/l. The intra- and interassay CVs for samples with values of 0.2–2.0 nmol/l were 7% and 9%, respectively. The reference range for healthy individuals after a 12-h fast was 0.25–0.75 nmol/l. The method for analysing C-peptide was changed in May 2002 (Immulite; DPC Diagnostic Products Corporation, Los Angeles, CA, USA) and the reference values after that were 0.3–1.3 nmol/l. No conversion factor was available between the two methods, but we have still chosen to include all C-peptide values when presenting mean C-peptide values [14].

The Västerbotten cohort GAD65A levels were analysed using a radiobinding assay in which full-length human GAD65 was labelled with [^{35}S] methionine, as described elsewhere [16, 17]. The results were expressed as IU/ml. All samples with CV values greater than 20% were reanalysed. The intra- and interassay CVs were 6% and 9%, respectively. In the Diabetes Antibody Standardization Program 2007 workshop, GAD65A analysis had 82% sensitivity and 96% specificity [16]. The analysis was performed at the laboratory of Professor Åke Lernmark, Clinical Research Centre at Lund University, Skåne University Hospital, Malmö, Sweden. GAD65A was considered positive when levels exceeded 32.0 IU/ml. This level represented the 97.5th percentile for 400 healthy blood donors [18]. HbA_{1c} was analysed with the same method as in the Skåne cohort [14].

Statistical analysis

Data are shown as numbers, proportions, means±SD or medians (interquartile range [IQR]). Differences in means for continuous variables were analysed by independent Student's *t* test; differences in medians were analysed using the Mann–Whitney test, and differences in proportions using the χ^2 test. Bivariate and multivariate logistic regression analysis was performed to identify determinants of poor glycaemic control at follow-up. ORs and 95% CIs were calculated. Only variables that were significant in the bivariate analysis were entered into the multivariate analysis. We performed a sensitivity analysis by excluding LADA patients with the lowest third of GAD65A from one of our calculations.

Values of $p < 0.05$ were considered statistically significant. The statistical analysis was performed with SPSS (www-01.ibm.com/software/analytics/spss/downloads.html).

Results

Characteristics of the Skåne and Västerbotten cohorts

In total, there were 372 patients with LADA and 372 with type 2 diabetes in our study (Table 1). The Skåne cohort contributed the majority of the study population (73%). Patients with LADA had lower BMIs at both diagnosis and follow-up compared with patients with type 2 diabetes.

There was no difference in HbA_{1c} values between individuals with LADA and with type 2 diabetes at diagnosis, but patients with LADA had higher HbA_{1c} values at follow-up (Table 1). Time to initiation of insulin therapy was shorter and

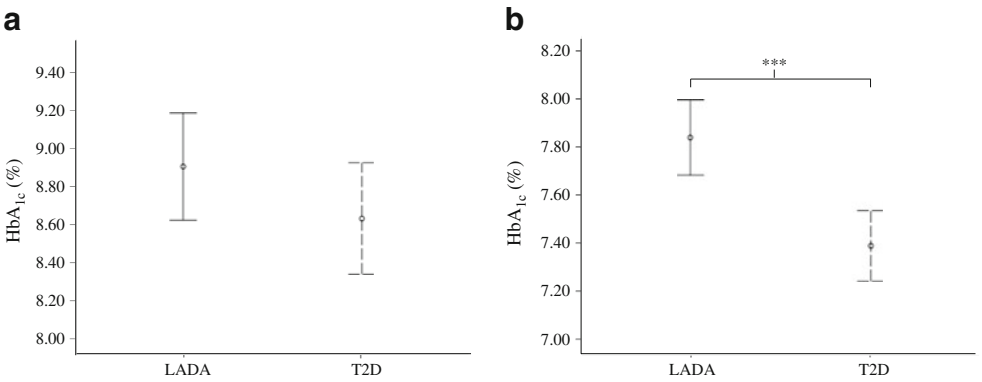

Fig. 1 Mean HbA_{1c} and 95% CI (indicated by the error bar) at (**a**) diagnosis and (**b**) follow-up for patients with LADA (solid line) and with type 2 diabetes (T2D; broken line). ***$p<0.001$. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

duration of insulin therapy longer among patients with LADA, while patients with type 2 diabetes were treated for a longer time with diet and exercise, OHAs and combination therapy (Table 1). As depicted in Fig. 1a, mean HbA_{1c} did not differ at diagnosis, whereas patients with LADA had higher mean HbA_{1c} values at follow-up (Fig. 1b). The proportions of patients with poor glycaemic control did not differ at diagnosis (LADA 70.3% vs type 2 diabetes 64.6%; p=NS), but more LADA patients (67.8%) had poor glycaemic control at follow-up compared with type 2 diabetes patients (53.0%; $p<0.001$).

The likelihood of poor glycaemic control was significantly elevated for patients with LADA compared with those with type 2 diabetes, increased significantly with increasing HbA_{1c} at diagnosis and decreased significantly with increasing age at diagnosis (Table 2).

As the cut-off for defining LADA was arbitrary, we also carried out a sensitivity analysis. In this sensitivity analysis, the main result remained: patients with LADA still had worse glycaemic control at follow-up than patients with type 2 diabetes even after excluding those whose GAD65A values were in the lowest tertile (data not shown).

Discussion

In this observational retrospective cohort study, individuals with LADA had worse glycaemic control at follow-up than those with type 2 diabetes, as well as a longer duration of insulin treatment, which might indicate a more severe form of diabetes. Although glycaemic control at follow-up was also influenced by HbA_{1c} at diagnosis, adjustment for age and BMI at diagnosis, the follow-up time did not change the fact that LADA patients had worse glycaemic control than type 2 diabetes patients.

This conclusion was not affected by GAD65A concentrations, as shown in our sensitivity analysis. Moreover, in contrast to physicians in Västerbotten, their colleagues in Skåne had access to GAD65A and C-peptide analyses shortly after their patients had been diagnosed. However, the time to initiation of insulin treatment in those LADA was about the same in the two cohorts, suggesting that most clinicians did not consider GAD65A levels or C-peptide when customising insulin treatment.

Our findings are in line with those of two observational studies [2, 5] that did not observe any better effect of insulin than of oral hypoglycaemic therapy on glycaemic control in LADA. These results differ from those of two small randomised studies from Japan in which early insulin treatment

Table 2 Bivariate and multivariate logistic regression analysis of likelihood of poor glycaemic control ($HbA_{1c}\geq7.0\%$ [53 mmol/mol]) at follow-up

Characteristic	Categories	HbA_{1c}		Bivariate analysis		Multivariate logistic regression	
		<7.0 (n=287)	≥7.0 (n=438)	OR	95% CI	OR	95% CI
Type of diabetes							
	T2D	170	192	1		1	
	LADA	117	246	1.86	1.38, 2.52	1.81	1.22, 2.68
Age at diagnosis (years)		287	438	0.96	0.94, 0.97	0.96	0.94, 0.98
Total insulin (months)		265	413	1.01	1.01, 1.02	1.00	1.00, 1.01
Cohort							
	Skåne	210	323	1			
	Västerbotten	77	115	0.97	0.69, 1.36		
HbA_{1c} at diagnosis		253	332	1.25	1.16, 1.35	1.24	1.14, 1.35
Follow-up time (months)		265	413	1.01	1.01, 1.01	1.00	1.00, 1.01
BMI at diagnosis		265	373	0.98	0.95, 1.01		

T2D, type 2 diabetes

was associated with improved beta cell function and sustained glycaemic control compared with treatment with a sulfonylurea [6, 7]. The negative effect of sulfonylurea on glycaemic control in patients with LADA was confirmed in a recent Cochrane meta-analysis [19]. This review also pointed out a number of weaknesses in the LADA studies. First, all the studies were very small and had short follow-up times. Second, the definition of LADA differed considerably between the studies, making comparisons difficult.

We cannot exclude the possibility that our results would have been different if our LADA patients had received insulin even earlier, as suggested by the studies from Japan. However, their results could not be confirmed by Borg et al as they did not find any beneficial effects of early insulin treatment in patients with preserved beta cell function at diagnosis [20]. This is consistent with our finding of a lack of reduction in HbA_{1c} at follow-up in patients with LADA who received early insulin treatment. However, our study was not designed to determine whether patients would benefit from early insulin treatment.

It has been proposed that LADA patients with high concentrations of GAD65A are more similar to individuals with type 1 diabetes than are those with low GAD65A concentrations [21]. If this were true, one could assume that the patients with LADA in our study with high GAD65A concentrations would have benefitted from an earlier initiation of insulin treatment. However, this assumption was not supported by the result of our sensitivity analysis.

A strength of this study is that it included one of the largest unselected LADA populations ever described. It is also the first study of patients treated in a clinical setting. The main weakness of our study is the retrospective data collection from regular medical charts, resulting in a high proportion of missing values for the patient characteristics at diagnosis (HbA_{1c} and BMI) and a lack of information on insulin doses and C-peptide levels. This might raise the alternative hypothesis that worse glycaemic control is likely to be accounted for by an earlier and quicker loss of residual beta cell function, a lack of timely initiation of insulin treatment and inappropriate intensification of insulin treatment afterwards. Moreover, different methods were used when analysing GAD65A, and different cut-off values were used within our cohorts. However, a strong linear correlation between the different methods has been demonstrated [18]. Finally, we did not have information on other autoantibodies (e.g. IA-2A, IAA) or T cell data.

Conclusion

Patients with LADA in the current study show worse glycaemic control than do patients with type 2 diabetes despite a longer time on insulin therapy. This suggests that better validated treatment strategies are required in the treatment of LADA.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement CDA acquired, analysed and interpreted the data, and co-wrote the draft of the manuscript. LB analysed and interpreted the data, and co-wrote the draft of the manuscript. LN analysed the data and revised the manuscript. UL made a substantial contribution to the design of the study and revised the manuscript. EL acquired data and drafted the manuscript. LG was one of the designers of the study, interpreted data and drafted the manuscript. OR was one of the designers of the study, analysed and interpreted data, and drafted the article. All authors approved the final version of the manuscript.

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