

INFLUENCE OF FAMILY HISTORY OF DIABETES ON INCIDENCE AND PREVALENCE OF LATENT AUTOIMMUNE DIABETES OF THE ADULT (LADA). RESULTS FROM THE NORD-TRØNDELAG HEALTH STUDY

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ABSTRACT

OBJECTIVE

The aim of this study was to investigate the association between family history of diabetes (FHD) and prevalence and incidence of LADA, type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

The results were based on cross-sectional data from 64,498 men and women ≥ 20 years in the Nord-Trøndelag Health Study, including 128 cases of LADA; 1,134 cases of type 2 and 123 cases of type 1 diabetes. In addition, prospective data on 46,210 subjects, including 80 incident cases of LADA, observed between 1984-86 and 1995-97 were available. Patients with LADA had antibodies against GAD and were insulin independent at diagnosis.

RESULTS

FHD was associated with a 4 times (Odds Ratio (OR) =3.92, 95% CI=2.76-5.58) increased prevalence of LADA. Corresponding estimates for type 2 diabetes and type 1 diabetes were 4.2 (95% CI=3.72-4.75) and 2.78 (95% CI=1.89-4.10), respectively. LADA patients with FHD had lower levels of C-peptide (541 vs. 715 pmol/l) and were more often insulin treated (47 % vs. 31%), than patients without FHD. Prospective data indicated that subjects with siblings with diabetes had a 2.5 (95% CI=1.39-4.51) times increased risk of developing LADA during the 11-year of follow-up compared to those without.

CONCLUSIONS

This study indicates that FHD is a strong risk factor for LADA and that the influence of family history may be mediated through a heritable reduction of insulin secretion.

Latent autoimmune diabetes of the adult (LADA) is a common form of diabetes, but the risk factors are less well understood than for type 1 and for type 2 diabetes [1], including the impact of family history of diabetes (FHD). Familial clustering of diabetes is believed to be due to a combination of shared genetic and environmental factors. For type 1 diabetes, the genetic influence has been located to the histocompatibility (HLA) region of chromosome 6 [2] whereas for type 2 diabetes, the genetic background remains largely unknown. Studies indicate that LADA has the same genetic features characteristics of type 1 diabetes, including an increased frequency of HLA-DQB1 genotypes [3-4]. On the other hand, results from a British study indicated that 33% of LADA patients have relatives with type 2 diabetes [5]. These findings suggest that LADA may share inherited features with both type 1 and type 2 diabetes.

Epidemiological studies indicate a 3-4 times increased risk of type 2 diabetes in subjects with close relatives with diabetes [6-8]. For type 1 diabetes, a 15 times increased risk has been reported in siblings of diabetes patients [2]. The risk of type 1 and type 2 diabetes is known to increase with an increasing number of affected relatives [6-7, 9]. It has also been shown that the risk varies depending on which relative(s) has diabetes. For type 1 diabetes, several studies have shown that having a father with diabetes is associated with a higher risk than having a mother with diabetes [10]. For type 2 diabetes on the other hand, some studies have suggested a preferential maternal effect [7, 11]. To what extent the risk of LADA is influenced by family history of diabetes is largely unknown.

The Nord-Trøndelag Health Survey (HUNT) is a large, population-based study where cases of diabetes have been classified according to clinical history and presence or absence of GAD antibodies. We will use this

data to investigate the influence of FHD on the prevalence and incidence of LADA compared to type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Nord-Trøndelag health survey

HUNT 1

From 1984 to 1986, all inhabitants of the Norwegian county of Nord-Trøndelag who were aged 20 years or older were invited to take part in the Nord-Trøndelag Health Study (HUNT 1) ($n=85,100$) [12]. The survey featured a clinical examination, including measurements of height, weight and blood pressure, and questionnaires with questions on current health, diabetes and lifestyle factors such as smoking and alcohol consumption. Of those invited, 90.3% participated ($n=76,885$).

HUNT 2

Between 1995 and 1997 a second health survey ($n=92,703$) was conducted in Nord-Trøndelag (HUNT2), again including all inhabitants aged 20 years or older. The overall response rate in this follow-up investigation was 71.3% ($n=65,258$) [13]. The clinical investigation included height, weight, blood pressure, waist and hip circumference, HDL-cholesterol, cholesterol, triglycerides and glucose. In addition to the questions used at HUNT 1 this questionnaire included more detailed information on FHD.

Study population

The analyses of this paper were based on cross-sectional data from 64,833 men and women who participated in HUNT2 with complete information on FHD, age and sex. In addition there were prospective data from 41,548 subjects who participated in both investigations and were free from diabetes at the baseline investigation.

Family history of diabetes

Detailed information on FHD was available from the HUNT 2 questionnaire, including separate questions on diabetes in the mother, father, brothers and sisters and children together with age at onset for each relative. In addition information on diabetes in siblings was available from the baseline questionnaire.

Body mass index and smoking

Based on measures of height and weight taken at the clinical investigations at HUNT 2 we calculated BMI as kg/m^2 . Information on current and previous smoking was used to classify subjects as never, former and current smokers.

Identification of diabetes cases

The HUNT 2 questionnaire identified 1,951 cases of diabetes. These subjects were given an appointment to have their fasting blood glucose measured together with levels of C-peptide and anti-GAD. Information on treatment was also collected. Altogether 1,454 (74.5%) patients completed this second investigation.

Patients starting insulin treatment within 6 months of diagnosis were classified as having type 1 diabetes, if, in addition, they were anti-GAD positive or had fasting C-peptide levels lower than 150 pmol/l ($n=123$). Patients were classified as having LADA if they were anti-GAD positive and had not been treated with insulin within 12 months of diagnosis ($n=128$). Type 2 diabetes cases were anti-GAD negative and without insulin treatment within 1 year of diagnosis ($n=1,134$). Out of the 1,454 cases, 845 were incident cases of diabetes, i.e. subjects diagnosed during the follow-up period between HUNT 1 and HUNT 2. Among these were 80 cases of LADA, 744 cases of type 2 diabetes and 21 cases of type 1 diabetes.

Biochemical analyses

Anti-GAD and fasting C-peptide was analysed at the Hormone Laboratory of Aker

University Hospital, Oslo. Anti-GAD was analysed by an immunoprecipitation radioligand assay based on a previously validated method [14] and the results expressed as antibody index (ai). The latter was calculated as (counts in the patient sample minus counts in a negative reference serum) divided by (counts in a reference antibody-containing serum minus counts in a negative reference serum). The assay was tested for proficiency in a current diabetes autoantibody standardisation programme. At the cut-off level of more than 0.08, sensitivity was 0.64 and specificity 1.00. Analysis of C-peptide was done by RIA (Diagnostic System Laboratories, Webster, Tex., USA).

Statistical analyses

Characteristics of the participants were expressed as means and standard deviations (SD). C-peptide was not normally distributed and therefore expressed as median and interquartile range. P-values were calculated with Student *t* test and Kruskal-Wallis's test (C-peptide) for means and with Chi-2 test for proportions. Analyses of FHD and the prevalence of LADA, type 1 and type 2 diabetes were performed based on cross-sectional data from HUNT 2. In addition, we investigated the influence of having siblings with diabetes on the cumulative incidence of diabetes, i.e. the risk of developing diabetes during the 11 year follow-up period between HUNT 1 and HUNT 2. To assess the association between FHD and prevalence and incidence of LADA, type 1 and type 2 diabetes, we calculated odds ratios (ORs) together with 95% confidence intervals (CIs) using multiple logistic regression analysis (Proc Logistic, SAS/STAT; SAS Institute, Cary, N.C., USA). Confounding was adjusted for by inclusion of age and sex in the regression model. Additional adjustment for BMI and smoking did not change the ORs (change <10%) and these variables were therefore not included in the final model.

The Regional Ethical Committee for Medical Research and the Norwegian Data Inspectorate approved these studies. All participants gave informed consent.

RESULTS

Subjects with LADA and type 2 diabetes were similar in most of the characteristics recorded (table 1). They were on average 20 years older, had higher BMI, WHR and blood pressure and less favourable levels of blood lipids than subjects with type 1 diabetes and those without diabetes. More than 40% of the LADA and type 2 diabetes cases reported FHD compared to 31% of type 1 diabetes cases and 15% of subjects without diabetes.

There were no clear differences between LADA patients with and without FHD with regard to age at investigation, age at onset, diabetes duration, body mass index, blood pressure or lipids (table 2). However, LADA patients with FHD had lower titres of anti-GAD than those without FHD. In addition, they seemed to have lower levels of C-peptide and more often be treated with insulin. Subjects with type 2 diabetes and FHD were marginally younger, leaner; more often treated with insulin and had lower C-peptide levels than those without FHD. With regard to type 1 diabetes, subjects with FHD seemed to be younger at onset and have higher BMI and anti-GAD than those without FHD.

Subjects with a family member with diabetes were almost 4 times as likely to have LADA (table 3) compared to subjects without FHD. Similar results were seen for type 2 diabetes and type 1 diabetes. There was no indication of gender differences in the influence of FHD on the occurrence of LADA or type 2 diabetes. However, for type 1 diabetes, men with diabetes in the family had an OR of 3.75, 95% CI=2.29-6.14 whereas the corresponding estimate in women was 1.81, 95% CI=0.96-3.42.

Having any family member with diabetes was associated with increased prevalence of LADA and type 2 diabetes (table 3). In contrast, type 1 diabetes was much more common in subjects with diabetes in siblings than in those with parents with diabetes. The occurrence of LADA was twice as high in subjects with male relatives compared to those with female relatives (OR=1.98, 95% CI=1.07-3.66). For type 2 diabetes and type 1 diabetes, there seemed to be no systematic differences between having female and male relatives with diabetes.

The prospective data (table 4) showed that the risk of developing LADA and type 2 diabetes during the 11-year follow-up was 2.5 and 2.1 times increased, respectively, in subjects who at baseline reported having a sibling with diabetes. The risk of type 1 diabetes was more than 7 times increased in those with siblings with diabetes.

CONCLUSIONS

We found by analysis of cross-sectional data that LADA was four times more common in subjects with FHD. In addition, prospective data showed that subjects with siblings with diabetes were twice as likely to develop LADA during the 11-year follow-up compared to those without FHD. Together, these findings demonstrate that FHD is a risk factor for LADA of the same magnitude as for type 2 diabetes.

With regard to type 2 diabetes, our study confirms previous findings indicating a 4 times increased prevalence in subjects with FHD [6-8]. For type 1 diabetes, the association with FHD was weak compared to previous data [2]. One reason may be that the majority of our type 1 diabetes cases (66%) had onset at age 20 or above. The genetic background may be stronger in subjects with early onset type 1 diabetes [15]. Accordingly, we found that 40 % of subjects with onset of type 1 diabetes before the age of 20 had FHD compared to 25% of those with onset during adulthood.

Previous reports have shown that the risk of both type 1 and type 2 diabetes increases with number of affected relatives [6-7, 9]. Our study extends these findings to LADA by showing a 6 times increased prevalence in subjects with more than one relative with diabetes.

LADA and type 2 diabetes subjects with FHD had lower levels of C-peptide and were more often treated with insulin than those without FHD, despite having the same duration of diabetes. This suggests that FHD influences the risk of LADA by way of reduced insulin secretion, and that this situation is shared with subjects with type 2 diabetes. Notably, the differences in C-peptide and insulin treatment were substantial but only significant for type 2 diabetes and not for LADA: Still our findings are consistent with previous reports of impaired insulin secretion in the offspring of LADA patients [18].

Previous information on the role of FHD in the aetiology of LADA is sparse. In a British study, 33% of LADA patients had diabetes in close relatives [5]. This figure was somewhat lower than in our study (43%) which may be explained by the fact that Castleden et al excluded subjects whose relatives had type 1 diabetes. As far as we know, only two previous studies have compared FHD in subjects with type 2 diabetes and LADA and the results of these studies were not consistent; Castleden et al [5] reported a higher proportion with FHD in type 2 patients than in LADA patients whereas the opposite was found in an Icelandic study [19]. Unfortunately, these studies did not include type 1 diabetes. Our findings suggest that the role of FHD is equally strong for type LADA as for type 2 diabetes but stronger than for type 1 diabetes; since only 31 % of type 1 diabetes cases had FHD compared to 43% of LADA patients.

Subjects with male relatives with diabetes were twice as likely to have LADA as those

with female relatives. This corresponds to previous findings in type 1 diabetes [10]. Several explanations behind this phenomenon have been proposed including a higher rate of miscarriage in women with type 1 diabetes [17]. Notably, no difference between maternal or paternal diabetes on the risk of type 1 diabetes was seen in the present study. This may be explained by the fact that we, for the most part, investigated cases with onset during adulthood where the association with parental diabetes was weak.

For type 1 diabetes having a sibling with diabetes, carried a much greater risk than having parents with diabetes. This is in accordance with results from the Diabetes Prevention Trial 1 [16]. It could mean that the family environment shared by siblings is particularly important for evolution of type 1 diabetes. However, it should be noted that our type 1 cases were on average almost 20 years younger than our LADA and type 2 cases. Hence, the parents may not have yet developed diabetes.

We found that LADA patients with FHD had lower levels of anti-GAD than subjects without FHD. This confirms findings by Castleden et al. who reported that FHD was less common in LADA cases with anti-GAD levels in the highest tertile [5]. A tentative explanation could be that less autoimmune activity is required to cause LADA in individuals with genetic susceptibility to diabetes (i.e. genetic susceptibility of a kind that is unrelated to autoimmunity). In this context we note that LADA patients with high anti-GAD (highest 50%) were on average 6 years younger at onset of diabetes than those with low anti-GAD (results not shown), indicating that age-related insulin resistance was strongest in those with low anti-GAD.

Recent studies have shown that type 1 and type 2 diabetes often occur in the same families, indicating partly common genetic background [20]. In the present study, we did not have information on the type of

diabetes in relatives. We did find that none of the parents of our LADA patients had onset of diabetes before the age of 40 even though this does not exclude autoimmune diabetes. We also found that subjects with LADA and type 2 diabetes were similar in phenotype and in associations with FHD. These observations indicate at least a partly common genetic background for LADA and type 2 diabetes.

The main results of this study may be afflicted with recall bias as they were based on cross-sectional data. This may have resulted in an overestimation of the association between FHD and diabetes. Our findings were however, supported by prospective data indicating an increased incidence of diabetes in subjects reporting siblings with diabetes. The sensitivity of 64% of our anti-GAD assay means that some cases of LADA could be classified as cases of type 2 diabetes. Still, even though this would reduce the power of our LADA analyses, it would not bias the relative risk estimates for LADA as long as the under

diagnosis was not related to FHD. Finally, it should be mentioned that FHD reflects not solely genetic influences but a combination of shared genetic and environmental effects.

In summary, the results of this study demonstrate that FHD is a strong risk factor for LADA, and indicates a partly common genetic background with type 2 diabetes than type 1 diabetes. Further, the influence of family history may be mediated through a heritable reduction of insulin secretion.

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Table 1. Characteristics of participants of the Nord-Trøndelag Health Study 1995-1997 (HUNT 2).

	No known diabetes N=63,113	LADA N=128	Type 2 diabetes N=1,134	Type 1 diabetes N=123
% men	46.8 %	53.1 %	49.3 %	59.4 %
% with FHD	14.6 %*	43.0 %	44.6%	30.9%#
Mean age (years) (SD)	49.4 (17.1)*	68.2 (11.8)	68.1 (11.1)	48.7 (16.2)#
Mean BMI (kg/m ²) (SD)	26.3 (4.05) *	28.5 (4.7)	29.6 (4.8)§	26.1 (3.9)#
Mean WHR (SD)	0.84 (0.08) *	0.89 (0.07)	0.90 (0.08)	0.85 (0.07)#
Mean systolic blood pressure (mm Hg) (SD)	131.5 (19.3) *	147.7 (23.3)	148.3 (22.2)	134.1 (19.1)#
Mean diastolic blood pressure (mm Hg) (SD)	82.6 (11.0) *	89.8 (12.3)	90.5 (10.9)	83.6 (9.8)#
Mean HDL cholesterol (mmol/l) (SD)	1.38 (0.39) *	1.24 (0.47)	1.19 (0.38)	1.57 (0.45)#
Mean cholesterol (mmol/l) (SD)	5.89 (1.26)	5.87 (1.28)	6.25 (1.28)§	5.55 (1.16)#
Mean triglycerides (mmol/l) (SD)	1.74 (1.11) *	2.29 (1.44)	2.60 (1.55)§	1.34 (0.71)#

* P-value <0.05 for difference between subjects with LADA and subjects without known diabetes

§ P-value <0.05 for difference between subjects with LADA and subjects with type 2 diabetes

p-value <0.05 for difference between subjects with LADA and subjects with type 1 diabetes

Table 2. Characteristics of subjects with LADA, type 2 diabetes and type 1 diabetes by Family history of diabetes (FHD). The HUNT 2 Study 1995-97.

	LADA			TYPE 2 DIABETES			TYPE 1 DIABETES		
	No FHD	FHD	<i>P</i>	No FHD	FHD	<i>P</i>	No FHD	FHD	<i>p</i>
No.	73 (57.0 %)	55 (43.0%)		628 (55.4%)	506 (44.6%)		85 (69.1%)	38 (30.9%)	
% men	56.2%	49.1%	0.4273	51.6%	46.4 %	0.0847	56.5 %	65.8%	0.3309
Mean age (years) (SD)	68.2 (12.3)	68.1 (11.1)	0.4397	69.0 (11.3)	67.1 (10.5)	0.0185	47.1 (12.3)	52.4 (16.8)	0.5878
Mean BMI (kg/m ²) (SD)	28.0 (4.4)	29.1 (5.0)	0.3140	29.7 (4.8)	29.4 (4.8)	0.8777	25.5 (3.6)	27.4 (4.2)	0.2725
Mean WHR (SD)	0.89 (0.07)	0.90 (0.08)	0.3896	0.90 (0.08)	0.89 (0.08)	0.4779	0.83 (0.06)	0.87 (0.08)	0.0527
Mean Diastolic blood pressure (mm Hg) (SD)	90.5 (12.3)	89.0 (12.3)	0.9846	91.2 (11.0)	89.5 (10.6)	0.3522	84.4 (10.3)	82.0 (8.7)	0.3072
Mean Systolic blood pressure (mm Hg) (SD)	149.1 (24.2)	145.8 (22.1)	0.4917	150.0 (23.0)	146.4 (20.9)	0.0290	134.7 (19.8)	132.8 (17.8)	0.5375
Mean HDL cholesterol (mmol/l) (SD)	1.25 (0.47)	1.24 (0.48)	0.9298	1.18 (0.39)	1.21 (0.35)	0.0197	1.59 (0.47)	1.52 (0.42)	0.4008
Mean Cholesterol (mmol/l) (SD)	5.77 (1.22)	6.00 (1.36)	0.3854	6.26 (1.32)	6.24 (1.23)	0.1141	5.53 (1.14)	5.61 (1.21)	0.6734
Mean Triglycerides (mmol/l) (SD)	2.17 (1.32)	2.45 (1.59)	0.1417	2.70 (1.62)	2.46 (1.44)	0.0046	1.28 (0.70)	1.49 (0.72)	0.7840
Mean age at onset (SD)	57.4 (14.3)	57.4 (13.4)	0.6243	59.5 (14.8)	58.3 (12.8)	0.0016	29.5 (15.6)	26.1 (18.6)	0.2031
Mean duration (years) (SD)	10.6 (12.5)	10.5 (10.3)	0.1812	9.0 (12.1)	8.6 (10.2)	0.0002	17.4 (12.3)	24.7 (14.7)	0.1852
% with insulin treatment	31.5%	47.3%	0.0693	19.3%	23.5%	0.0815	100%	100%	
Median C-peptide (pmol) (interquartile range)	588.0 (798.0)	440.0 (606.0)	0.1110	783.50 (662.0)	728.0 (556.0)	0.0258	*	*	
Mean Anti-GAD (ai) (SD)	0.43 (0.60)	0.26 (0.34)	<0.0001	0.01 (0.02)	0.01 (0.02)	0.4655	0.29 (0.45)	0.44 (0.60)	0.0313

Table 3. Family history of diabetes (FHD) and odds ratio of prevalent LADA, type 2 and type 1 diabetes. The HUNT 2 Study 1995-97.

FHD	SUBJECTS NOT REPORTING DIABETES No.	Cases	LADA		TYPE 2 DIABETES			TYPE 1 DIABETES		
			OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
No	53,926	73	1.0		628	1.0		85	1.0	
Yes	9,187	55	3.92	2.76-5.58	506	4.20	3.72-4.75	38	2.78	1.89-4.10
One family member with diabetes	8,100	42	3.51	2.40-5.14	361	3.51	3.07-4.0	28	2.32	1.51-3.57
≥ two family members with diabetes	1,087	13	6.29	3.46-11.44	145	8.33	6.84-10.15	10	6.60	3.38-12.88
Mother with diabetes	3,965	18	3.34	1.99-5.62	238	5.17	4.42-6.06	10	1.67	0.86-3.23
Father with diabetes	2,678	15	5.66	3.21-9.99	96	4.29	3.42-5.38	7	1.68	0.78-3.65
Parents with diabetes	6,370	29	4.07	2.62-6.31	284	4.62	3.99-5.36	13	1.36	0.75-2.43
Sister with diabetes	1,264	12	3.59	1.93-6.69	117	4.01	3.24-4.95	13	7.79	4.20-14.44
Brother with diabetes	1,420	17	5.13	3.00-8.75	131	4.76	3.89-5.81	15	7.52	4.25-13.31
Siblings with diabetes	1,827	17	3.54	2.07-6.05	121	2.92	2.37-3.58	21	8.51	5.14-14.09
Children with diabetes	458	4	4.06	1.47-11.21	21	2.40	1.53-3.78	3	4.74	1.48-15.22
Mother or sister with diabetes	4,554	19	2.65	1.60-4.40	257	4.16	3.57-4.84	19	2.83	1.71-4.68
Father or brother with diabetes	3,472	23	5.15	3.21-8.27	137	3.58	2.95-4.34	16	3.02	1.77-5.17

Odds ratios were adjusted for age and sex of the participants

Table 4. Baseline information on diabetes in siblings (HUNT 1, 1984-86) and odds ratio of incident LADA, type 1 and type 2 diabetes during 11 years of follow-up (HUNT2 1995-97).

SIBLINGS WITH DIABETES	SUBJECTS NOT REPORTING DIABETES		LADA		TYPE 2 DIABETES			TYPE 1 DIABETES		
	No.	Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
No	38,759	65	1.0		617	1.0		17	1.0	
Yes	1,944	15	2.51	1.39-4.51	127	2.21	1.80-2.71	4	7.24	2.22-23.64

Odds ratios were adjusted for age and sex of the participants