Influence of Family History of Diabetes on Incidence and Prevalence of Latent Autoimmune Diabetes of the Adult

Results from the Nord-Trøndelag Health Study

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

RESEARCH DESIGN AND METHODS — The results were based on cross-sectional data from 64,498 men and women (aged ≥20 years) who were in the Nord-Trøndelag Health Study, which included 128 cases of LADA, 1,134 cases of type 2 diabetes, and 123 cases of type 1 diabetes. In addition, prospective data on 46,210 subjects, which included 80 incident cases of LADA, observed between 1984 and 1986 and 1995 and 1997 were available. Patients with LADA had antibodies against GAD and were insulin independent at diagnosis.

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

Diabetes Care 30:3040–3045, 2007

Latent autoimmune diabetes of the adult (LADA) is a common form of diabetes, but the risk factors, including the impact of family history of diabetes (FHD), are less well understood than those for type 1 and type 2 diabetes (1). 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 the genetic background for type 2 diabetes remains largely unknown. Studies indicate that LADA has the same genetic features characteristic 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 patients with LADA 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 three to four 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 diabetic 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 in which cases of diabetes have been classified according to clinical history and the presence or absence of GAD antibodies. We used these data to investigate the influence of FHD on the prevalence and incidence of LADA compared with those for type 1 and type 2 diabetes.

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Received for publication 12 April 2007 and accepted in revised form 12 September 2007.

Published ahead of print at http://care.diabetesjournals.org on 18 September 2007. DOI: 10.2337/dc07-0718.

Abbreviations: FHD, family history of diabetes; HUNT, Nord-Trøndelag Health Survey; LADA, latent autoimmune diabetes of the adult.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

HUNT 1

From 1984 to 1986, all inhabitants of the Norwegian county of Nord-Trøndelag who were aged ≥20 years were invited to take part in HUNT 1 (n = 85,100) (12). The survey featured a clinical examination, including measurements of height, weight, and blood pressure and question-

naires 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 (HUNT 2), again including all inhabitants aged ≥20 years. 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 in HUNT 1, this questionnaire included more detailed information on FHD.

Study population

The analyses in this article were based on cross-sectional data from 64,833 men and women who participated in HUNT 2 for whom complete information on FHD, age, and sex was available. In addition, prospective data from 41,548 subjects who participated in both investigations and were free from diabetes at the baseline investigation were included.

FHD

Detailed information on FHD was available from the HUNT 2 questionnaire, including separate questions on diabetes in 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.

BMI and smoking

Based on measures of height and weight taken at the clinical investigations in HUNT 2, we calculated BMI as weight in kilograms divided by the square of height in meters. 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$^+$ or had fasting C-peptide levels <150 pmol/l (n = 123). Patients were classified as having LADA if they were anti-GAD$^+$ and had not been treated with insulin within 12 months of diagnosis (n = 128). Type 2 diabetic subjects were anti-GAD$^-$ and had not received insulin treatment within 1 year of diagnosis (n = 1,134). 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 were analyzed at the Hormone Laboratory of Aker University Hospital, Oslo, Norway. Anti-GAD was analyzed by an immunoprecipitation radioligand assay based on a previously validated method (14), and the results are expressed as antibody index. The latter was calculated as (counts in the patient sample − counts in a negative reference serum)/(counts in a reference antibody-containing serum − counts in a negative reference serum). The assay was tested for proficiency in a current diabetes autoantibody standardization program. At the cutoff level of >0.08, sensitivity was 0.64 and specificity was 1.00. Analysis of C-peptide was done by a radioimmunoassay (Diagnostic System Laboratories, Webster, TX).

Statistical analyses

Data for characteristics of the participants are expressed as means ± SD. C-peptide was not normally distributed and therefore is expressed as median and interquartile range. P values were calculated with Student's t test (means), Kruskall-Wallis test (medians), and with a χ^2 test (proportions). Analyses of FHD and the prevalence of LADA, type 1 diabetes, and type 2 diabetes were performed on the basis of 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 diabetes, and type 2 diabetes, we calculated odds ratios (ORs) together with 95% CIs using multiple logistic regression analysis (Proc Logistic, SAS/STAT; SAS Institute, Cary, NC). Confounding was adjusted for by

Table 1—*Characteristics of participants in HUNT 2, 1995–1997*

	No known diabetes	LADA	Type 2 diabetes	Type 1 diabetes
n	63,113	128	1,134	123
Men (%)	46.8	53.1	49.3	59.4
FHD (%)	14.6*	43.0	44.6	30.9†
Age (years)	49.4 ± 17.1*	68.2 ± 11.8	68.1 ± 11.1	48.7 ± 16.2†
BMI (kg/m^2)	26.3 ± 4.05*	28.5 ± 4.7	29.6 ± 4.8‡	26.1 ± 3.9†
Waist-to-hip ratio	0.84 ± 0.08*	0.89 ± 0.07	0.90 ± 0.08	0.85 ± 0.07†
Systolic blood pressure (mmHg)	131.5 ± 19.3*	147.7 ± 23.3	148.3 ± 22.2	134.1 ± 19.1†
Diastolic blood pressure (mmHg)	82.6 ± 11.0*	89.8 ± 12.3	90.5 ± 10.9)	83.6 ± 9.8†
HDL cholesterol (mmol/l)	1.38 ± 0.39*	1.24 ± 0.47	1.19 ± 0.38	1.57 ± 0.45†
Cholesterol (mmol/l)	5.89 ± 1.26	5.87 ± 1.28	6.25 ± 1.28‡	5.55 ± 1.16†
Triglycerides (mmol/l)	1.74 ± 1.11*	2.29 ± 1.44	2.60 ± 1.55‡	1.34 ± 0.71†

Data are means ± SD, unless indicated otherwise. *P <0.05 for difference between subjects with LADA and subjects without known diabetes. †P < 0.05 for difference between subjects with LADA and subjects with type 1 diabetes. ‡P < 0.05 for difference between subjects with LADA and subjects with type 2 diabetes.

inclusion of age and sex in the regression model. Additional adjustment for BMI and smoking did not change the ORs (change <10%), and, therefore, these variables were 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, waist-to-hip ratio, and blood pressure; and had less favorable levels of blood lipids than subjects with type 1 diabetes and those without diabetes. More than 40% of the subjects with LADA and type 2 diabetes reported FHD compared with 31% of type 1 diabetic subjects and 15% of subjects without diabetes.

There were no clear differences between patients with LADA with and without FHD with regard to age at investigation, age at onset, diabetes duration, BMI, blood pressure, or lipids (Table 2). However, patients with LADA who had FHD had lower titers of anti-GAD than those without FHD. In addition, they seemed to have lower levels of C-peptide and more often were being treated with insulin. Subjects with type 2 diabetes and FHD were marginally younger and leaner, were 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 four times as likely to have LADA (Table 3) compared with subjects without FHD. Similar results were seen for type 2 and type 1 diabetes. There was no indication of sex 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 (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 rela-

Table 2—*Characteristics of subjects with LADA, type 2 diabetes, and type 1 diabetes by FHD: HUNT 2, 1995–1997*

	LADA			Type 2 diabetes			Type 1 diabetes		
	No FHD	FHD	*P* value	No FHD	FHD	*P* value	No FHD	FHD	*P* value
n (%)	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
Age (years)	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
BMI (kg/m^2)	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
Waist-to-hip ratio	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
Diastolic blood pressure (mmHg)	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
Systolic blood pressure (mmHg)	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
HDL cholesterol (mmol/l)	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
Cholesterol (mmol/l)	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
Triglycerides (mmol/l)	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
Age at onset (years	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)	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
Insulin treatment (%)	31.5	47.3	0.0693	19.3	23.5	0.0815	100	100	
C-peptide (pmol)	588.0 (798.0)	440.0 (606.0)	0.1110	783.50 (662.0)	728.0 (556.0)	0.0258	—*	—*	
Anti-GAD (antibody index)	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

Data are means ± SD or median (interquartile range) (for C-peptide), unless otherwise indicated. *Subjects with type 1 diabetes did not have measurable C-peptide levels.

Table 3—*FHD and ORs of prevalent LADA, type 2 diabetes, and type 1 diabetes: HUNT 2, 1995–1997*

FHD	Subjects not reporting diabetes	LADA		Type 2 diabetes		Type 1 diabetes	
		Cases	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 or more 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)

ORs were adjusted for age and sex of the participants.

tives having diabetes than for those with female relatives having diabetes (OR 1.98 [95% CI 1.07–3.66]). For type 2 and type 1 diabetes, there seemed to be no systematic differences between having female or 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 seven 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 who had siblings with diabetes were twice as likely to develop LADA during the 11-year follow-up compared with 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 four times increased prevalence in subjects with FHD (6–8). For type 1 diabetes, the association with FHD was weak compared with previous data (2). One reason may be that the majority of our type 1 diabetic subjects (66%) had onset at age ≥20. 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 with 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 six times increased prevalence in subjects with more than one relative with diabetes.

Subjects with LADA and type 2 diabetes 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 finding 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 patients with LADA (16).

Previous information on the role of FHD in the etiology of LADA is sparse. In a British study, 33% of patients with LADA had close relatives with diabetes (5). This figure was somewhat lower than that in our study (43%), which may be explained by the fact that Castleden et al. (5) excluded subjects whose relatives had type 1 diabetes. As far as we know, FHD in subjects with type 2 diabetes and LADA have been compared in only two previous studies, and the results of these studies were not consistent; Castleden et al. (5) reported a higher proportion of type 2 diabetic patients with FHD than of patients with LADA, whereas the opposite was found in an Icelandic study (17). Unfortunately, these studies did not include type 1 diabetes. Our findings suggest that the role of FHD is equally strong for LADA as for type 2 diabetes but stronger than for type 1 diabetes, because only

Table 4—*Baseline information on diabetes in siblings (HUNT 1, 1984–1986) and ORs of incident LADA, type 2 diabetes, and type 1 diabetes during 11 years of follow-up (HUNT 2, 1995–1997)*

Siblings with diabetes	Subjects not reporting diabetes	LADA		Type 2 diabetes		Type 1 diabetes	
		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)

ORs were adjusted for age and sex of the participants.

31% of type 1 diabetic patients had FHD compared with 43% of patients with LADA.

Subjects with male relatives with diabetes were twice as likely to have LADA as those with female relatives with diabetes. This observation 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 (18). Notably, no difference between maternal or paternal diabetes on the risk of type 1 diabetes was seen in the present study. This result may be explained by the fact that we, for the most part, investigated patients with onset during adulthood for which 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 observation is in accordance with results from the Diabetes Prevention Trial 1 (19). 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 diabetic subjects were on average almost 20 years younger than our subjects with LADA and type 2 diabetes. Hence, the parents may not have developed diabetes yet.

We found that patients with LADA who had FHD had lower levels of anti-GAD than subjects without FHD. This observation confirms findings of Castleden et al. (5) who reported that FHD was less common in patients with LADA who had anti-GAD levels in the highest tertile. 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 patients with LADA 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 in part a 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 in part a common genetic background for LADA and type 2 diabetes.

The main results of this study may be affected by recall bias as they were based on cross-sectional data, which may have caused an overestimation of the association between FHD and diabetes. Our findings were, however, supported by prospective data indicating increased incidence of diabetes in subjects reporting siblings with diabetes. The 64% sensitivity of our anti-GAD assay means that some cases of LADA could be classified as cases of type 2 diabetes. Still, even though this misclassification would reduce the power of our LADA analyses, it would not bias the relative risk estimates for LADA as long as the underdiagnosis was not related to FHD. Finally, it should be mentioned that FHD reflects not solely genetic influences but also 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 genetic background that may have more in common with type 2 diabetes than with type 1 diabetes. Further, the influence of family history may be mediated through a heritable reduction of insulin secretion.

Acknowledgments— HUNT is a collaboration between the HUNT Research Centre, Norwegian University of Science and Technology; the Norwegian Institute of Public Health, and the Nord-Trøndelag County Council. GlaxoSmithKline Norway and the Norwegian Diabetes Association supported HUNT. This particular study was supported by a grant from the Swedish Council for Working Life and Social Research.

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