Effect of Parental Type 2 Diabetes on Offspring With Type 1 Diabetes

Lena M. Thorn, md[1,2]
Carol Forsblom, md, dmsc[1,2]
Johan Wadén, md[1,2]
Jenny Söderlund, msc[1]
Milla Rosengård-Bärlund, md[1,2]
Markku Saraheimo, md[1,2]
Outi Heikkilä, md[1,2]
Kustaa Hietala, md[1,2]
Kim Pettersson-Fernholm, md, dmsc[2]
Jorma Ilonen, md, dmsc[3,4]
Per-Henrik Groop, md, dmsc[1,2]
on behalf of the FinnDiane Study Group

OBJECTIVE — The purpose of this study was to study the association between a parental history of type 2 diabetes and the metabolic profile as well as the presence of the metabolic syndrome and diabetes complications in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — This was a cross-sectional study design in 1,860 patients with type 1 diabetes from the Finnish Diabetic Nephropathy (FinnDiane) Study (620 patients with and 1,240 age-matched patients without a parental history of type 2 diabetes). Information on parental history was received from the type 1 diabetic offspring by a standardized questionnaire.

RESULTS — Patients with type 1 diabetes and a positive parental history of type 2 diabetes had a higher prevalence of the metabolic syndrome (44 vs. 38%; $P = 0.013$) and a metabolic profile related to insulin resistance (higher BMI, larger waist circumference, and higher triglycerides, A1C, and insulin dose per kilogram) and also had a later onset of type 1 diabetes (17.2 ± 9.2 vs. 16.1 ± 8.9 years; $P = 0.008$), which was also confirmed in the publicly available Diabetes Control and Complications Trial data set. In contrast, no association was observed with blood pressure, diabetes complications, or HLA genotype distribution. Parental history of type 2 diabetes was independently associated with age at onset of type 1 diabetes (odds ratio 1.02 [95% CI 1.01–1.03]), BMI (1.07 [1.02–1.12]), triglycerides (1.18 [1.03–1.35]), and insulin dose per kilogram (1.63 [1.04–2.54]).

CONCLUSIONS — Parental history of type 2 diabetes is associated with a later onset of type 1 diabetes, the metabolic syndrome, and a metabolic profile related to insulin resistance.

Diabetes Care **32:63–68, 2009**

Patients with type 1 diabetes have an increased risk of cardiovascular morbidity and mortality. This risk is to a large extent explained by the high cardiovascular risk attributed to diabetic nephropathy, but even patients without nephropathy have a fourfold increased risk of cardiovascular disease compared with individuals without diabetes (1). The metabolic syndrome, a constellation of cardiovascular risk factors (2), is itself a risk factor for cardiovascular disease and type 2 diabetes in the general population (3). It is noteworthy that metabolic syndrome is also a common finding in patients with type 1 diabetes (4), but its role as a cardiovascular risk factor in patients with type 1 diabetes is less clear (5).

The rapidly growing worldwide epidemic of type 2 diabetes has been explained by obesity and the sedentary lifestyle of humans in modernity. Although such environmental factors are undoubtedly important, familial factors also seem to play a major role in the pathogenesis of type 2 diabetes. Consequently, offspring of a parent with diabetes have a lifetime risk of type 2 diabetes of 40%, and when both parents have type 2 diabetes, the risk is even higher (6). It is also of note that even in families with a patient with type 1 diabetes, there is a higher proportion of relatives with type 2 diabetes (7). The fact that type 1 and type 2 diabetes cluster in families suggests that some patients may even have a "double form" of diabetes. However, so far there are no diagnostic procedures to find out whether a patient has had "two hits," but this may be shown through a metabolic profile that is related to insulin resistance and features of the metabolic syndrome in patients with type 1 diabetes.

However, data on the consequences of a family history of type 2 diabetes on the offspring with type 1 diabetes are still scarce. Some support of an effect of type 2 diabetes is provided by the Diabetes Control and Complications Trial (DCCT), in which improvement of glycemic control in the intensive treatment arm led to an increase in weight gain that was greatest in those with a positive family history of type 2 diabetes (8). Consequently, we hypothesized that parental history of type 2 diabetes may be associated with a metabolic profile related to insulin resistance, the metabolic syndrome, and the presence of late diabetes complications in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— This study is part of the ongoing nationwide Finnish Diabetic Nephropathy (FinnDiane) Study, with an aim of finding clinical, genetic, and environmental risk factors for micro- and macrovascular complications of type 1 diabetes. The present study has a cross-sectional study design. For this analysis, all patients with an age at onset of diabetes <35 years and insulin treatment initiated within 1 year of diagnosis and complete information on metabolic syndrome, renal status, and parental medical history were selected from the FinnDiane database ($n = 3,184$) in March 2006. Patients with a parental history of type 1 diabetes ($n = 89$) or an unknown type of parental diabetes ($n = 145$) were excluded. Of the

From the [1]Folkhälsan Institute of Genetics, Folkhälsan Research Center, Biomedicum Helsinki, Helsinki, Finland; the [2]Department of Medicine, Division of Nephrology, Helsinki University Hospital, Helsinki, Finland; the [3]Immunogenetics Laboratory, University of Turku, Turku, Finland; and the [4]Department of Clinical Microbiology, University of Kuopio, Kuopio, Finland.
Corresponding author: Per-Henrik Groop, per-henrik.groop@helsinki.fi.
Received 6 March 2008 and accepted 22 September 2008.
Published ahead of print at http://care.diabetesjournals.org on 3 October 2008. DOI: 10.2337/dc08-0472.

3,037 eligible patients, 620 had a positive parental history of type 2 diabetes. Those with a positive parental history of type 2 diabetes, compared with those with a negative parental history, were significantly older, and, therefore, of the 2,417 patients with a negative parental history of type 2 diabetes we randomly selected 1,240 control subjects of matching age. The matching for age was first done by dividing those with a positive parental history of type 2 diabetes into octiles regarding age. Those with a negative parental history of diabetes were then ordered by a random number from zero to one. Thereafter the control subjects were chosen in numerical order in a 1:2 ratio from each age-group.

The local ethics committees approved the study, and the study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Patients with type 1 diabetes

Data on medication, cardiovascular status, and diabetes complications of the patients with type 1 diabetes were registered with a standardized questionnaire, which was completed by the patient's attending physician. Coronary heart disease was defined as diagnosed myocardial infarction, coronary revascularization, or pharmacological treatment with long-acting nitroglycerin. Stroke was defined as cerebral infarction or intracerebral hemorrhage. Cardiovascular hard end points included diagnosed myocardial infarction, coronary revascularization, or stroke. Renal status was defined on the basis of the urinary albumin excretion rate in at least two of three overnight or 24-h urine collections: normal urinary albumin excretion (<20 μg/min or <30 mg/24 h [n = 920]), microalbuminuria (≥20 and <200 μg/min or ≥30 and <300 mg/24 h [n = 221]), macroalbuminuria (≥200 μg/min or ≥300 mg/24 h [n = 459]), or end-stage renal disease (undergoing dialysis or having a transplanted kidney [n = 260]). Diabetic nephropathy was defined as macroalbuminuria or end-stage renal disease. As a measure of insulin sensitivity, we used an equation for the estimated glucose disposal rate (eGDR) modified for use with A1C instead of HbA_1 (4). As another marker of insulin sensitivity, we used the total daily insulin dose per body weight. Metabolic syndrome was assessed according to both the National Cholesterol Education Program (NCEP) III criteria (9) and the International Diabetes Federation (IDF) definition (2). Anthropometric data (weight, height, and waist and hip circumferences) and blood pressure were collected by a trained nurse.

Assays

Fasting blood samples were drawn and analyzed for A1C and serum lipids and lipoproteins. A1C was determined by standardized assays at each center (normal range 4.0–6.0%) and serum lipid and lipoprotein concentrations were measured at the research laboratory of Helsinki University Central Hospital, Division of Cardiology (Helsinki, Finland) by automated enzymatic methods using a Cobas Mira analyzer (Hoffman-LaRoche, Basel, Switzerland).

HLA genotyping

HLA genotyping was performed for a random set of 1,136 patients, including 63% of those with a positive and 60% of those with a negative parental history of type 2 diabetes. HLA-DR and -DQ alleles were assessed as described earlier. HLA genotypes were divided into five risk categories based on the presence of various risks associated with type 1 diabetes and the observed genotype frequencies in 622 diabetic children and 622 affected family members based on artificial control subjects in a Finnish population (10).

Parental information

Parental information was obtained from the diabetic patients by a standardized questionnaire with an 89% sensitivity and 98% specificity to detect diabetes (11). History of diabetes was determined separately for each parent, and if the parent had diabetes, the age at onset and mode of treatment were registered. For the diagnosis of parental type 2 diabetes, an age at onset >50 years or treatment with oral hypoglycemic agents or diet was required. Of those 620 patients with a positive parental history of type 2 diabetes, 327 (53%) had a mother, 248 (40%) had a father, and 45 (7%) had both parents with type 2 diabetes. Those with both parents with diabetes were excluded from the subanalyses regarding maternal and paternal diabetes.

Replication in the DCCT

To replicate our findings, we also used the publicly available database of the DCCT (available at http://www.gcrc.umn.edu/gcrc/downloads/dcct.html). The same criteria as those for the present study were used for inclusion, that is, adult patients with type 1 diabetes with an age at onset of diabetes <35 years (n = 1,197). In the DCCT, family history of type 2 diabetes was defined as a first-degree relative with type 2 diabetes (8), and 119 patients had a positive family history.

Statistical analysis

The statistical significance of differences in categorical variables between groups was tested with a χ^2 test. Continuous variables were analyzed with a t test if normally distributed (results are presented as means ± SD) or Mann-Whitney U test if not normally distributed (presented as median with interquartile range). Logistic regression analyses were used to test which variables were independently associated with a parental history of type 2 diabetes. Results are presented as odds ratios (ORs) (95% CI). In the logistic regression analyses, we included variables with $P < 0.05$ in univariate analyses. All analyses were performed using SPSS (version 15.0; SPSS Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

RESULTS — We investigated the role of a parental history of type 2 diabetes in 1,860 patients with type 1 diabetes. The mean age of the patients with type 1 diabetes was 43.5 ± 10.1 years, and 50% were men. The characteristics of patients with and without a parental history of type 2 diabetes are shown in Table 1. Patients with a positive parental history of type 2 diabetes had a later onset of type 1 diabetes (Fig. 1), higher BMI, larger waist circumference, higher triglycerides, and higher A1C concentrations, whereas no difference was observed for blood pressure or prevalence of diabetes complications. The use of stricter criteria for type 1 diabetes defined as an age at onset <25 years did not change the result of a later onset of type 1 diabetes in offspring of parents with type 2 diabetes (13.3 ± 6.3 vs. 12.6 ± 6.2 years; P = 0.043), whereas in those with an age at onset <15 years there was no difference in the age at onset of type 1 diabetes (9.0 ± 3.8 vs. 8.8 ± 3.8 years; P = 0.411).

The frequency of parental type 2 diabetes increased with the number of components of the metabolic syndrome (29, 32, 35, 36, and 52% in those with one, two, three, four, and five components, respectively; P = 0.007). The NCEP score was associated with parental history of type 2 diabetes after adjustment for age at onset of diabetes, A1C, and insulin dose (OR 2.70 [95% CI 1.51–4.81], 5 vs. 1

Table 1—*Clinical characteristics of patients with type 1 diabetes grouped by parental history of type 2 diabetes*

	Negative parental history of type 2 diabetes	Positive parental history of type 2 diabetes	*P*	Positive maternal history of type 2 diabetes	*P*	Positive paternal history of type 2 diabetes	*P*
n	1,240	620		327		248	
Male sex	50	49	0.431	49	0.688	49	0.711
Age (years)	43.4 ± 10.0	43.9 ± 10.2	0.344	46.1 ± 10.1	<0.001	40.8 ± 9.7	<0.001
Age at onset of diabetes (years)	16.1 ± 8.9	17.2 ± 9.0	0.008	17.8 ± 9.2	0.002	16.5 ± 8.7	0.428
BMI (kg/m^2)	25.0 ± 3.5	25.7 ± 3.8	<0.001	25.7 ± 3.7	0.001	25.6 ± 3.8	0.010
Waist circumference (cm)	86.1 ± 11.5	88.0 ± 12.0	0.002	88.2 ± 12.2	0.005	87.6 ± 11.8	0.066
HDL cholesterol (mmol/l)	1.38 ± 0.44	1.37 ± 0.46	0.478	1.37 ± 0.45	0.686	1.36 ± 0.47	0.424
Triglycerides (mmol/l)	1.01 (0.75–1.39)	1.06 (0.80–1.62)	0.001	1.10 (0.81–1.63)	<0.001	1.02 (0.76–1.58)	0.160
A1C	8.3 ± 1.3	8.4 ± 1.4	0.028	8.5 ± 1.4	0.004	8.2 ± 1.4	0.727
eGDR (mg · kg^{-1} · min^{-1})	5.6 (4.1–8.1)	5.3 (3.9–7.9)	0.055	5.1 (3.8–7.5)	0.004	5.9 (4.3–8.0)	0.553
Insulin dose (IU/kg)	0.65 ± 0.21	0.68 ± 0.26	0.008	0.68 ± 0.26	0.071	0.70 ± 0.26	0.005
Systolic blood pressure (mmHg)	137 ± 19	138 ± 19	0.195	139 ± 19	0.082	136 ± 20	0.771
Diastolic blood pressure (mmHg)	80 ± 10	80 ± 10	0.570	80 ± 9	0.489	79 ± 10	0.854
Antihypertensive medication	49	49	0.974	52	0.439	45	0.194
Coronary heart disease	7.4	9.9	0.070	12	0.005	5.8	0.376
Cardiovascular end points	12	13	0.442	17	0.013	7.7	0.058
Diabetic nephropathy	38	40	0.297	41	0.346	38	0.981
Microalbuminuria	12	13	0.510	12	0.964	15	0.135
Retinal laser treatment	44	44	0.892	48	0.214	40	0.260
Metabolic syndrome IDF	38	43	0.029	46	0.007	36	0.684
Metabolic syndrome NCEP	38	44	0.013	44	0.030	42	0.215

Data are means ± SD, median (interquartile range), or percentages unless otherwise indicated. *P* values represent comparisons with negative parental history of type 2 diabetes.

point of the metabolic score and 1.16 [1.04–1.28], the metabolic score analyzed as a continuous variable). Metabolic syndrome itself showed a weak association with parental history of type 2 diabetes (Table 1) and was not significant after adjustment for age at onset of diabetes, A1C, and insulin dose (data not shown). Patients with a positive parental history of type 2 diabetes had also a higher insulin dose per body weight ($P = 0.008$) and showed a tendency to be more insulin resistant as defined by a lower eGDR ($P = 0.055$) (Table 1).

In a multivariate analysis, parental history of type 2 diabetes was independently associated with age at onset of type 1 diabetes (OR 1.02 [95% CI 1.01–1.03]), BMI (1.07 [1.02–1.12]), triglycerides (1.18 [1.03–1.35]), and insulin dose per body weight (1.63 [1.04–2.54]) but not with waist circumference, A1C, or the NCEP metabolic syndrome.

Maternal history of type 2 diabetes

Factors associated with a maternal history of type 2 diabetes are shown in Table 1. Those with a positive maternal history of type 2 diabetes were older than those with a negative maternal history. In the age-adjusted logistic regression analysis, a positive maternal history was independently associated with a later onset of type 1 diabetes (OR 1.02 [1.01–1.03]), higher BMI (1.07 [1.02–1.13]), higher triglycerides (1.18 [1.01–1.38]), higher A1C concentration (1.11 [1.01–1.22]), and higher insulin dose per body weight (1.81 [1.02–3.23]) but not with waist circumference, cardiovascular hard end points, or the IDF metabolic syndrome. We excluded eGDR from the model because A1C and waist circumference are included in the formula for eGDR. If eGDR, however, was included and A1C and waist circumference were excluded from the model, eGDR was not independently associated with a parental history of type 2 diabetes.

Paternal history of type 2 diabetes

In the univariate analysis, only a higher BMI and a higher insulin dose per body weight were associated with a positive paternal history of type 2 diabetes. Those with a positive paternal history were, however, notably younger compared with those with a negative paternal history (Table 1). In a multivariate age-adjusted model, an independent association with a paternal history of type 2 diabetes was found for both insulin dose per body weight (OR 1.86 [1.02–3.37]) and BMI (1.05 [1.01–1.09]).

HLA

In the 1,136 patients with data on HLA available, our typing method identified 23 different haplotypes. The most common haplotypes found, with >1% frequency, are listed in supplemental Table 1 (available in an online appendix at http://dx.doi.org/10.2337/dc08-0472). DRB1*0401-DQB1*0302 and (DR7)-DQA1*0201-DQB1*02 (3.6% vs. 1.9%; $P = 0.011$) were slightly more common among those with a positive parental history of type 2 diabetes (35 vs. 30%; $P = 0.015$), whereas (DR3)-DQA1*05-DQB1*02 (20 vs. 24%; $P = 0.033$) was more common among those with a negative parental history. These differences were not significant after correction for the number of comparisons. The 85 different HLA genotypes identified were

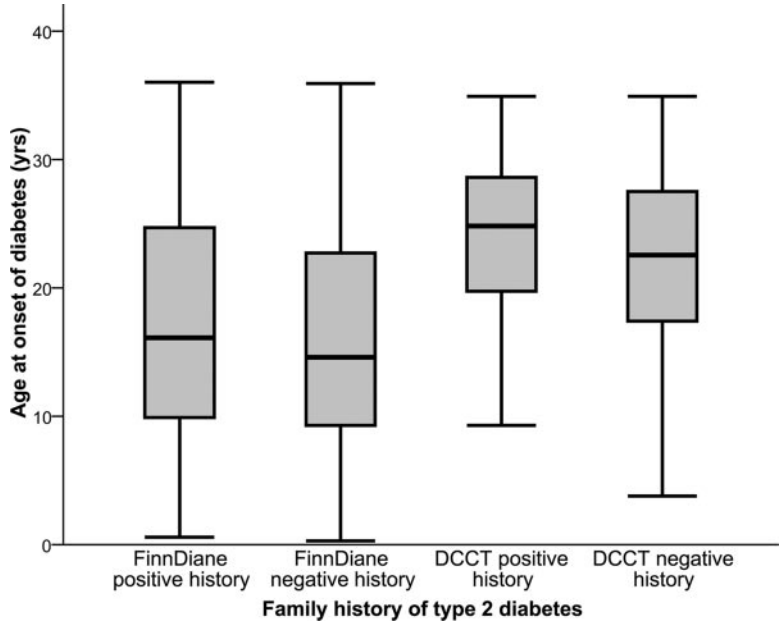

Figure 1—*Distribution of age at onset of type 1 diabetes in individuals with a positive family history of type 2 diabetes compared with those with a negative family history in the FinnDiane Study (17.2 ± 9.0 vs. 16.1 ± 8.9 years;* P *= 0.008) and in the DCCT cohort (23.9 ± 6.5 vs. 22.2 ± 6.8 years;* P *= 0.008).*

classified according to the conferred risk for type 1 diabetes, and the distribution was similar to that of another Finnish population of patients with type 1 diabetes (10). No differences in the distribution between patients with or without a parental history of type 2 diabetes were found (supplemental Table 2 available in an online appendix).

Replication in the DCCT

In the DCCT, patients with type 1 diabetes and a positive family history of type 2 diabetes had a later onset of type 1 diabetes compared with those with a negative family history (23.9 ± 6.5 vs. 22.2 ± 6.8 years; $P = 0.008$) (Fig. 1). The association of later onset of type 1 diabetes and positive family history of type 2 diabetes was also significant after adjustment for BMI, triglycerides, insulin dose, and A1C (data not shown).

CONCLUSIONS — In the present study of patients with type 1 diabetes, a positive parental history of type 2 diabetes was associated with a later onset of type 1 diabetes, the metabolic syndrome, and a metabolic profile related to insulin resistance. To our knowledge, this is the first study to show that a positive parental history of type 2 diabetes is associated with the metabolic syndrome in patients with type 1 diabetes. The association was weak when the metabolic syndrome was analyzed as a dichotomous variable but strong when it was analyzed as a continuous score. The finding fits well with data from nondiabetic offspring of patients with type 2 diabetes who are more insulin resistant and show components of the metabolic syndrome (12). In addition, the present study showed an independent association between a parental history of type 2 diabetes and a higher BMI, higher triglyceride concentrations, and a higher insulin dose in favor of a worse metabolic profile, suggesting the presence of insulin resistance. Previous studies assessing the role of a parental history of type 2 diabetes in patients with type 1 diabetes are few, have had their main focus on diabetes complications, and have only presented univariate data regarding metabolic profiles. However, in these studies, a positive family history of type 2 diabetes was associated with various disturbances in the lipid profile (8,13), whereas data regarding hypertension, obesity, A1C, and insulin dose have been conflicting (8,13–16). Notably, in the present large-scale study we were also able to detect subtle changes in the metabolic profile, and this may be the reason that we were able to show a more comprehensive picture of the metabolic disturbances.

In this study, a positive parental history of type 2 diabetes was not associated with the presence of late diabetes complications. However, a positive maternal history of type 2 diabetes was associated with a higher prevalence of cardiovascular hard end points and coronary heart disease, although the association was not significant in the age-adjusted multivariate analysis. Previous studies have indeed shown an association with intermediate markers of cardiovascular disease such as carotid intima-media thickness (17) as well as with cardiovascular disease itself (13). Regarding microvascular complications, a family history of type 2 diabetes has been associated with diabetic retinopathy (18) and with diabetic nephropathy in some (13–15,18) but not all (11) studies. In the present study we did not observe any association between a parental history of type 2 diabetes and microvascular complications despite a long duration of type 1 diabetes and despite differences in the metabolic risk profile. These findings are somewhat surprising, and the question of why the unfavorable metabolic risk profile does not translate into microvascular complications arises. One explanation may be that the treatment of patients with diabetes has improved during recent years, with most guidelines recommending effective cardio- and renoprotective therapies at an early stage. This strategy may postpone the development of diabetes complications or even prevent the development of complications despite high risk and eventually lead to dilution of the data.

In patients with type 2 diabetes, a family history of the same trait results in an earlier onset of diabetes (19), which has been suggested to reflect a stronger genetic susceptibility. Our results, however, show a later onset of type 1 diabetes in those with a positive parental history of type 2 diabetes. It could be argued that this finding is due to inclusion of patients with type 2 diabetes in the study population. However, this does not seem to be the answer. First, we have used rather strict criteria for type 1 diabetes, and even after the use of more stringent criteria such as an age at onset of diabetes of <25 years, there was still a later onset of type 1 diabetes in those with a positive parental history of type 2 diabetes, although the difference disappeared in those with an age at onset of <15 years. Second, the fact that the HLA genotype distribution did not differ between the groups and resembled that of a childhood-onset type 1 diabetes population speaks in favor of a true "type 1" population. Furthermore, the findings are also in line with those of a small Lebanese study on children, in

which a family history of type 2 diabetes was associated with a later onset of type 1 diabetes despite similar HLA genotypes (20). Third, we were also able to replicate the finding in the publicly available DCCT data set. Interestingly, the accelerator hypothesis suggests that obesity and insulin resistance result in an earlier onset of diabetes (21). In light of this theory, one would expect patients with type 1 diabetes and a positive family history of type 2 diabetes to develop diabetes at an earlier age compared with those with a negative family history of type 2 diabetes. This study does not, however, support such a view.

In type 2 diabetes there is an excess maternal transmission of type 2 diabetes, and there are also different consequences of paternal and maternal type 2 diabetes (22). In type 1 diabetes, this issue was previously addresses in only one small study. Hadjadj et al. (16) showed an association between maternal history of type 2 diabetes and diabetic nephropathy, as well as with insulin resistance and lower HDL cholesterol in offspring with type 1 diabetes, whereas paternal type 2 diabetes was associated with a higher BMI and larger waist circumference. In the present study we aimed to assess whether there is a different effect of maternal and paternal type 2 diabetes in a larger setting, and the results indicate a slightly worse metabolic profile in those with a positive maternal compared with paternal history of type 2 diabetes. These results should, however, be interpreted with caution, because the patients with a paternal history of type 2 diabetes were 5 years younger than those with a maternal history and age-adjustment in the statistical analyses could not entirely exclude a potential age bias. Furthermore, there was not sufficient power for the subanalyses because of the lower number of patients.

Our study design does not give an answer to what in fact is inherited from the parent with type 2 diabetes, i.e., genes or the environment, but certainly both play a role. One interesting point that may dilute our data is that the type 2 diabetes seen in the parents of patients with type 1 diabetes might represent a different kind of disease. In accordance, a higher proportion of GAD antibodies and high-risk HLA genotypes have been observed in patients with type 2 diabetes in mixed type 1 and 2 families (23). In this study, we unfortunately did not have data on HLA genotypes or GAD antibodies in the parents. This study also has some other limitations. The information on parental type 2 diabetes was received from the type 1 diabetic patients by a questionnaire and not first hand from the parents themselves. The questionnaire has, however, been validated and has a sufficient sensitivity to detect diabetes. The age matching, compared with age adjustment, might dilute the data. However, because the age-difference was rather large between those with and without a positive parental history of type 2 diabetes, matching was considered more appropriate. Notably, irrespective of the method chosen, the results are similar (data not shown). In light of earlier studies in nondiabetic subjects, it would have been more informative to have a direct measure of insulin sensitivity (clamp) in patients with type 1 diabetes, but this procedure was not feasible in this large data set.

In summary, parental history of type 2 diabetes is associated with a later onset of type 1 diabetes, the metabolic syndrome, and a metabolic profile related to insulin resistance.

Acknowledgments— The study was supported by grants from the Folkhälsan Research Foundation, Wilhelm and Else Stockmann Foundation, Liv och Hälsa Foundation, Finnish Medical Society (Finska Läkaresällskapet), Perklén Foundation, and European Commission (QLG2-CT-2001-01669 and LSHB-CT-2003-503364).

No potential conflicts of interest relevant to this article were reported.

The skilled technical assistance of Sinikka Lindh, Anna Sandelin, Susanne Ström, Jessica Thorn, Hannele Hildén, Helinä Perttunen-Mio, and Virve Naatti is gratefully acknowledged. Finally, we acknowledge all the physicians and nurses at each center participating in the collection of patients (presented in detail in an online appendix). We thank the DCCT investigators for making their trial data set public and therefore allowing independent investigators to analyze their work for the benefit of patients with type 1 diabetes.

Parts of this study were presented in abstract form at the 42nd annual meeting of the European Association for the Study of Diabetes, Copenhagen, Denmark, 14–17 September 2006 (*Diabetologia* 49 [Suppl. 1]:190, 2006).

References

1. Borch-Johnsen K, Kreiner S: Proteinuria: value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. *BMJ* 294:1651–1654, 1987
2. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome—a new worldwide definition. *Lancet* 366:1059–1062, 2005
3. Grundy SM: Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *J Am Coll Cardiol* 47: 1093–1100, 2006
4. Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, Waden J, Ronnback M, Rosengard-Barlund M, Bjorkesten CG, Taskinen MR, Groop PH: Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control (the FinnDiane study). *Diabetes Care* 28:2019–2024, 2005
5. Pambianco G, Costacou T, Orchard TJ: The prediction of major outcomes of type 1 diabetes: a 12-year prospective evaluation of three separate definitions of the metabolic syndrome and their components and estimated glucose disposal rate: the Pittsburgh Epidemiology of Diabetes Complications Study experience. *Diabetes Care* 30:1248–1254, 2007
6. Köbberling J, Tillil H: Empirical risk figures for first degree relatives of non-insulin dependent diabetics. In *Serono Symposium No. 47. The Genetics of Diabetes Mellitus.* Köbberling J, Tattersall R, Eds. London, Academic Press, 1982, p. 201–209
7. Dahlquist G, Blom L, Tuvemo T, Nystrom L, Sandstrom A, Wall S: The Swedish childhood diabetes study—results from a nine year case register and a one year case-referent study indicating that type 1 (insulin-dependent) diabetes mellitus is associated with both type 2 (non-insulin-dependent) diabetes mellitus and autoimmune disorders. *Diabetologia* 32:2–6, 1989
8. Purnell JQ, Dev RK, Steffes MW, Cleary PA, Palmer JP, Hirsch IB, Hokanson JE, Brunzell JD: Relationship of family history of type 2 diabetes, hypoglycemia, and autoantibodies to weight gain and lipids with intensive and conventional therapy in the Diabetes Control and Complications Trial. *Diabetes* 52:2623–2629, 2003
9. Executive summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
10. Hermann R, Turpeinen H, Laine AP, Veijola R, Knip M, Simell O, Sipila I, Akerblom HK, Ilonen J: HLA DR-DQ-encoded genetic determinants of childhood-onset type 1 diabetes in Finland: an analysis of 622 nuclear families. *Tissue Antigens* 62: 162–169, 2003
11. Thorn LM, Forsblom C, Fagerudd J, Pettersson-Fernholm K, Kilpikari R, Groop PH: Clustering of risk factors in parents of patients with type 1 diabetes and nephropathy. *Diabetes Care* 30:1162–1167, 2007
12. Eriksson J, Franssila-Kallunki A, Ek-

strand A, Saloranta C, Widén E, Schalin C, Groop L: Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med* 321:337–343, 1989
13. Erbey JR, Kuller LH, Becker DJ, Orchard TJ: The association between a family history of type 2 diabetes and coronary artery disease in a type 1 diabetes population. *Diabetes Care* 21:610–614, 1998
14. Fagerudd JA, Pettersson-Fernholm KJ, Grönhagen-Riska C, Groop P-H: The impact of a family history of type II (non-insulin-dependent) diabetes mellitus on the risk of diabetic nephropathy in patients with type I (insulin-dependent) diabetes mellitus. *Diabetologia* 42:519–526, 1999
15. Roglic G, Colhoun HM, Stevens LK, Lemkes HH, Manes C, Fuller JH, EURODIAB IDDM Complications Study Group: Parental history of hypertension and parental history of diabetes and microvascular complications in insulin-dependent diabetes mellitus: the EURODIAB IDDM Complications Study. *Diabet Med* 15:418–426, 1998
16. Hadjadj S, Duengler F, Torremocha F, Faure-Gerard G, Bridoux F, Boissonnot M, Mauco G, Guilhot J, Marechaud R: Maternal history of type 2 diabetes is associated with diabetic nephropathy in type 1 diabetic patients. *Diabetes Metab* 33:37–43, 2007
17. Makimattila S, Ylitalo K, Schlenzka A, Taskinen MR, Summanen P, Syvanne M, Yki-Jarvinen H: Family histories of type II diabetes and hypertension predict intima-media thickness in patients with type I diabetes. *Diabetologia* 45:711–718, 2002
18. Monti MC, Lonsdale JT, Montomoli C, Montross R, Schlag E, Greenberg DA: Familial risk factors for microvascular complications and differential male-female risk in a large cohort of American families with type 1 diabetes. *J Clin Endocrinol Metab* 92:4650–4655, 2007
19. Li H, Isomaa B, Taskinen M-R, Groop L, Tuomi T: Consequences of a family history of type 1 and type 2 diabetes on the phenotype of patients with type 2 diabetes. *Diabetes Care* 23:589–594, 2000
20. Zalloua PA, Shbaklo H, Halaby G, Terwedow H, Xu X, Azar ST: Type-2 diabetes family history delays the onset of type-1 diabetes. *J Clin Endocrinol Metab* 87: 3192–3196, 2002
21. Wilkin TJ: The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. *Diabetologia* 44:914–922, 2001
22. Groop L, Forsblom C, Lehtovirta M, Tuomi T, Nissén M, Ehrnström B-O, Forsén B, Isomaa B, Snickars B, Taskinen M-R: Metabolic consequences of a family history of NIDDM (the Botnia Study): evidence for sex-specific parental effects. *Diabetes* 45:1585–1593, 1996
23. Li H, Lindholm E, Almgren P, Gustafsson A, Forsblom C, Groop L, Tuomi T: Possible human leukocyte antigen-mediated genetic interaction between type 1 and type 2 diabetes. *J Clin Endocrinol Metab* 86:574–582, 2001