Different Patterns of Insulin Resistance in Relatives of Type 1 Diabetic Patients With Retinopathy or Nephropathy

The Genesis France-Belgium Study

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OBJECTIVE — Insulin resistance may be a risk factor for diabetic microangiopathy, which may have a familial component. We carried out a family-based study to determine which components of the insulin resistance syndrome are associated with diabetic retinopathy and nephropathy in type 1 diabetes.

RESEARCH DESIGN AND METHODS — The Genesis France-Belgium Study is a multicenter binational study designed to investigate the genetic factors involved in the microvascular complications of type 1 diabetes using a family-based design. Probands were type 1 diabetic patients with diabetic retinopathy (classified as background, preproliferative, or proliferative) and possibly diabetic nephropathy (absent, incipient, established, or advanced). The insulin resistance score of their first-degree relatives was calculated according to their BMI and history of arterial hypertension, lipid disorders, and type 2 diabetes.

RESULTS — The insulin resistance score of relatives was positively correlated with the albumin excretion rate ($P = 0.0009$) and fasting plasma glucose ($P = 0.0003$) and HbA_{1c} ($P < 0.0001$) concentrations. This score was higher in the relatives of probands with than in those without diabetic nephropathy ($P = 0.0370$). Similarly, it was higher in relatives of subjects with proliferative diabetic retinopathy than in those of probands without, even after controlling for subjects with versus without diabetic nephropathy ($P = 0.0379$). However, the components of the insulin resistance score in relatives differed according to the severity of diabetic retinopathy or nephropathy in the probands. Obesity and history of arterial hypertension were most common in relatives of probands with proliferative diabetic retinopathy, whereas obesity and history of lipid disorders were most common in the relatives of probands with diabetic nephropathy.

CONCLUSIONS — Familial insulin resistance segregates with diabetic complications: lipid disorders and obesity segregate with diabetic nephropathy, whereas arterial hypertension and obesity segregate with diabetic retinopathy.

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Microvascular complications are the hallmark of type 1 diabetes. Diabetic retinopathy is the most common sight-threatening disease in developed countries (1). Diabetic nephropathy is associated with increased mortality and cardiovascular morbidity (2,3).

Epidemiological studies (4,5) have revealed a familial predisposition to diabetic nephropathy. Parental predisposition to cardiovascular morbidity and mortality (6,7), arterial hypertension (8–10), and kidney disease (11,12) is likely to play a role in this predisposition to diabetic nephropathy. However, the exact determinants are still poorly understood. Familial predisposition to retinopathy also has been evidenced in diabetes (13), particularly to proliferative retinopathy in type 1 diabetic patients (14). Family-based studies make it possible to identify clinical features in relatives that could be altered by the disease in patients. Therefore, they are a valuable tool for testing pathophysiological hypotheses.

According to the definitions of the National Cholesterol Education Program (15) and the World Health Organization (WHO) (16), insulin resistance syndrome is characterized by a cluster of cardiovascular risk factors that can be easily assessed in clinical practice. These factors include hypertension (17), dyslipidemia (18), familial history of type 2 diabetes

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*A complete list of Genesis France-Belgium Study members can be found in the APPENDIX.

Abbreviations: AER, albumin excretion rate; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; UAE, urinary albumin excretion; WHO, World Health Organization.

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

(19), and obesity (20,21). Interestingly, these are also risk factors for the development and progression of microvascular complications, suggesting that insulin resistance plays a key role in microvascular complications (22).

Insulin resistance is a key feature of type 2 diabetes (23). However, according to longitudinal prospective studies (24,25), it is also a risk factor for diabetic retinopathy and nephropathy in type 1 diabetic patients. Only small studies (26–28) have tried to determine whether familial insulin resistance is a key determinant of familial predisposition to diabetic renal complications, but none have examined the link between familial insulin resistance and diabetic retinopathy. We analyzed whether insulin resistance in first-degree relatives of type 1 diabetic patients is associated with various stages of diabetic retinopathy and nephropathy in a large family-based study.

RESEARCH DESIGN AND METHODS

— The Genesis France-Belgium Study is a prospective, multicenter, family-based study, the main aim of which is to study the genetic determinants of diabetic nephropathy and retinopathy in type 1 diabetes. Between November 1998 and December 2000, 662 subjects with type 1 diabetes (defined by age at onset ≤35 years, with initial ketosis and requirement for permanent insulin treatment within 1 year of diagnosis) were recruited in 38 diabetes or nephrology clinics in France and Belgium. The present article is limited to the the 275 type 1 diabetic patients for which familial data are available (referred to as probands). Patients were recruited according to their renal status and family structure. Probands classified as positive for diabetic nephropathy had type 1 diabetes for ≥5 years, background or more severe diabetic retinopathy (see classification below), and incipient, established, or advanced nephropathy (see classification below). Probands classified as negative for diabetic nephropathy had type 1 diabetes for ≥20 years, with background or more severe retinopathy but without kidney disease (see classification below). Probands (diabetic nephropathy–positive case subjects and –negative control subjects) were only included if their two parents were alive (trio families) or if one parent and at least one sibling were alive (pseudotrio families). Some complex families were also recruited. They consisted of at least three family members, including one index not considered simply as trio or pseudotrio (e.g., one diabetic sibpair plus both parents). The study design was approved by the ethics committee of Angers University Hospital. All study participants (patients and relatives) gave written informed consent.

Type 1 diabetic patients were examined by their diabetes specialist in their diabetes clinic (or by their nephrologist if they were being treated for renal failure), and their first-degree relatives were examined by their regular physician. History of arterial hypertension, dyslipidemia, myocardial infaction, stroke, heart failure, and end-stage renal disorder was recorded.

Blood pressure was determined using a mercury sphygmomanometer after a 5-min rest in the sitting position. Body weight and height were measured in light clothes without shoes. A resting electrocardiogram was recorded for all type 1 diabetic patients. During medical visits, 10 ml urine was collected for albumin excretion rate (AER) determination and 38 ml blood for serum and plasma storage and DNA extraction.

Classification of diabetic nephropathy

Nephropathy was staged for probands by an independent adjudication committee, as previously described (29), using the patient's medical records and the three highest urinary AERs recorded in the patient's records during the previous 10 years as well as the antihypertensive treatment and the last plasma creatinine measurement. No nephropathy was classified as persistent normoalbuminuria (median of three urinary AER samples <20 mg/l or 20 μg/min or 30 mg/24 h) without antihypertensive treatment, including ACE inhibitors or angiotensin-II blockers. Incipient nephropathy was classified as persistent microalbuminuria (median of three urinary AER samples 20–200 mg/l or 20–200 μg/min or 30–300 mg/24 h). Established nephropathy was classified as persistent proteinuria (median of three urinary AER samples >200 mg/l or 200 μg/min or 300 mg/24 h) with plasma creatinine <150 μmol/l. Advanced nephropathy was classified as increased AER and plasma creatinine ≥150 μmol/l and/or renal replacement therapy. Case subjects had nephropathy (incipient, established, or advanced), and control subjects did not have nephropathy.

Classification of diabetic retinopathy

Retinopathy was staged by an independent adjudication committee according to Kohner's (30) classification, using the data obtained by direct funduscopy after pupil dilatation and/or fluorescein angiography. Stage 1 diabetic retinopathy (background retinopathy) was determined by three or more microaneurysms with or without hard exsudates and/or hemorrhages, stage 2 (preproliferative retinopathy) by intraretinal microvascular abnormalities and/or cotton wood exsudates, and stage 3 (proliferative retinopathy) by new vessels and/or past or present laser panphotocoagulation.

Insulin resistance score

Insulin resistance was assessed in relatives according to WHO recommendations (16). Hypertension, personal history of lipid disorders, personal history of type 2 diabetes, and obesity were considered. The insulin resistance score was calculated as follows.

Hypertension. Relatives received 0 points if they did not have a history of hypertension and 1 point if they did have a history of hypertension (systolic [SBP]/diastolic blood pressure >140/80 mmHg at physical examination and/or antihypertensive treatment) (31).

Lipid disorders. Relatives received 0 points if they did not have a history of dyslipidemia and 1 point if they had a lipid disorder (total cholesterol >6 mmol/l and/or fasting triglycerides >2.3 mmol/l) or were on hypolipidemic treatment.

Type 2 diabetes. Relatives received 1 point if they had a personal history of type 2 diabetes (23) (regardless of diabetes treatment) and 0 points otherwise.

Obesity. Relatives received 0 points if their weight was normal (BMI <25 kg/m^2), 0.5 points if they were overweight (BMI 25–29.9 kg/m^2), and 1 point if they were obese (BMI >30 kg/m^2). Due to missing data, the total was divided by the number of available items. Thus, the insulin resistance score ranged from 0 to 1 and was expressed in arbitrary units.

Biological determinations

HbA_{1c} was measured by high-performance liquid chromatography (Diamat;

Table 1—*Clinical and biological characteristics according to the severity of diabetic nephropathy in probands*

	Proband diabetic nephropathy stage				
	Absent	Incipient	Established	Advanced	*P*
n (%)	145	63	33	34	
Sex (M/F)	76/69	27/36	16/17	22/12	0.02196*
Age (years)	41 ± −9	39 ± 8	41 ± 9	42 ± 8	0.1846†
Diabetes duration (years)	26 ± 8	22 ± 8	25 ± 8	27 ± 8	0.0072†
BMI (kg/m^2)	24.2 ± 3.2	24.8 ± 4.1	25.2 ± 3.6	23.7 ± 3.5	0.2073†
HbA_{1c} (%)	8.5 ± 1.3	8.6 ± 1.4	8.4 ± 1.2	8.1 ± 1.4	0.4358†
Daily insulin dose (IU · kg body wt^{-1} · day^{-1})	0.69 ± 0.20	0.76 ± 0.27	0.66 ± 0.26	0.64 ± 0.22	0.0380‡
SBP (mmHg)	126 ± 17	131 ± 19	134 ± 20	155 ± 26	<0.0001†
DBP (mmHg)	73 ± 9	76 ± 11	79 ± 10	85 ± 12	<0.0001†
Serum creatinine (μmol/l)	78 (46–116)	79 (42–106)	98 (52–149)	212 (150–832)	<0.0001‡
Retinopathy stage (1/2/3)	82/29/34	25/16/22	7/5/21	1/6/27	<0.0001*

Data are means ± SD or median (range). *χ^2 test, †ANOVA, ‡Kruskal-Wallis test. Retinopathy stages are 1 (background)/2 (preproliferative)/3 (proliferative). DBP, diastolic blood pressure.

Biorad, Ivry-sur-Seine, France) (normal values 4–6%). Serum creatinine was measured using a modified version of Jaffe's method. Urinary albumin concentration was determined using a nephelometric method (32) on sterile urine (verified by dipstick test). Plasma glucose concentration was determined by using an enzymatic peroxidase method. Fasting serum insulin was determined in non–type 1 diabetic first-degree relatives using an immunoradiometric assay method (Bi-Insulin IRMA; Schering, Gif-sur-Yvette, France), allowing for the calculation of homeostasis model assessment of insulin resistance (HOMA-IR) (33).

Statistical analysis

Data are presented as means ± SD or median (range), if not normally distributed. Categorical variables were compared by using the χ^2 test and the χ^2 test for trend (34). ANOVA and Kruskal-Wallis were used to compare continuous variables according to index microvascular stages in probands or in relatives. A nonparametric Spearman test was used for correlation analyses. To take intrafamilial correlations into account, we used the PROC MIXED software for continuous variables and ran generalized estimating equations as implemented in the PROC GENMOD software for categorical variables. Statview 5.1 and SAS 8.2 (SAS Institute, Cary, NC) were used for calculations. Statistical significance was set at 0.05.

RESULTS — A total of 853 subjects were recruited in the Genesis France-Belgium Family Study (578 relatives and 275 probands; 130 probands with and 145 without diabetic nephropathy). Control families included 120 trios, 22 pseudotrios, and 3 complex families (5 of 306 relatives had type 1 diabetes). Case families included 105 trios, 17 pseudotrios, and 8 complex families (there were 15 subjects with type 1 diabetes among 272 relatives). In total, 269 mothers, 239 fathers, and 70 siblings were analyzed. The familial structure (mothers, fathers, siblings) did not differ between case and control subjects (χ^2 = 0.107, P = 0.9481).

Microvascular complications in probands

The characteristics of probands according to nephropathy stage are summarized in Table 1. As expected, SBP and the proportion of patients with proliferative retinopathy increased with severity of nephropathy. BMI did not differ according to severity of nephropathy.

The characteristics of probands according to their diabetic retinopathy stage are summarized in Table 2. Systolic blood pressure differed significantly according to retinopathy stage. Diabetes duration was longer in patients with proliferative retinopathy compared with other subjects. BMI did not differ between groups.

Familial data

Mean age was 70 ± 9, 68 ± 9, and 47 ± 10 years in fathers, mothers, and siblings, respectively. Type 2 diabetes was found in 44 subjects. History of arterial hypertension was found in 200 subjects, and a personal history of dyslipidemia was found in 190 relatives. Histories of diabetes and hypertension were closely related (χ^2 = 7.139, $P < 0.0001$), unlike histories of diabetes and dyslipidemia (χ^2 = 0.774, P = 0.3488). Myocardial infarction was found in 39 subjects and was more frequent in relatives with type 2 diabetes than in nondiabetic relatives (χ^2 = 7.069, P = 0.0078). In relatives who gave a blood sample in the fasting state (n = 358), who were not different from nonfasting relatives regarding age (P = 0.89), insulin resistance score (P = 0.57), or BMI (P = 0.69), the insulin resistance score was positively correlated with fasting insulinemia (ρ = 0.109, P = 0.0469) and HOMA-IR (ρ = 0.184, P = 0.0028). The insulin resistance score was positively correlated with HbA_{1c} in relatives (ρ = 0.284, $P < 0.0001$), even after exclusion of type 2 diabetic relatives. The insulin resistance score was also correlated with urinary albumin excretion (UAE) (ρ = 0.144, P = 0.0009).

UAE was higher in relatives of proband case subjects with incipient, established, or advanced diabetic nephropathy (8 mg/l [2–1,126]) than in relatives of control subjects without diabetic nephropathy (6 mg/l [2–640], P = 0.0176). The UAE in relatives was not associated with retinopathy severity in probands (data not shown).

The clinical and biological characteristics of first-degree relatives according to proband nephropathy stage are summarized in Table 3. Insulin resistance scores were significantly higher in first-degree relatives of nephropathic (0.37 ± 0.26) than in those of nonnephropathic (0.31 ±

Table 2—*Clinical and biological characteristics according to the severity of diabetic retinopathy in probands*

	Proband diabetic retinopathy stage			
	Stage 1	Stage 2	Stage 3	*P*
n (%)	115	56	104	
Sex (M/F)	63/52	33/23	45/59	0.1029*
Age (years)	41 ± 9	42 ± 9	40 ± 8	0.5555†
Diabetes duration (years)	23.8 ± 7.7	24.1 ± 7.7	26.9 ± 8.3	0.0112†
BMI (kg/m^2)	24.7 ± 3.6	24.6 ± 3.5	23.9 ± 3.4	0.2446†
HbA_{1c} (%)	8.3 ± 1.2	8.7 ± 1.5	8.4 ± 1.4	0.1968†
Daily insulin dose (IU · kg body wt^{-1} · day^{-1})	0.71 ± 0.21	0.76 ± 0.26	0.66 ± 0.22	0.0335‡
SBP (mmHg)	127 ± 20	136 ± 20	135 ± 22	0.0132†
DBP (mmHg)	75 ± 10	77 ± 11	77 ± 11	0.4300†
Serum creatinine (μmol/l)	79 (18–172)	74 (28–846)	96 (37–902)	<0.0001‡
Diabetic nephropathy stage (abs/inc/est/adv)	82/25/7/1	29/16/5/6	34/22/21/27	<0.0001*

Data are means ± SD or median (range). *χ^2 test, †ANOVA, ‡Kruskal-Wallis test. Diabetic retinopathy stages 1, 2, and 3 are background, preproliferative, and proliferative, respectively. Diabetic nephropathy stages are abs (absent)/inc (incipent)/est (established)/adv (advanced). DBP, diastolic blood pressure.

0.25, $P = 0.0370$) probands. The frequency of lipid disorders in relatives increased with the nephropathy stage of the proband. No such relationship was found with regard to history of type 2 diabetes or hypertension when fathers and mothers were analyzed separately. SBP and BMI did not differ in relatives according to the nephropathy stage of the proband ($F = 0.956$, $P = 0.4132$ and $F = 1.676$, $P = 0.1710$, respectively). However, maternal SBP increased with the severity of diabetic nephropathy in type 1 diabetic offspring ($F = 3.836$, $P = 0.0104$). Systolic blood pressure was higher in mothers of nephropathic (137 ± 17 mmHg) than nonnephropathic (132 ± 14 mmHg, $P = 0.0071$) probands.

The clinical and biological characteristics of relatives according to proband retinopathy stage are summarized in Table 4. The insulin resistance scores of relatives depended on retinopathy severity. The insulin resistance scores of relatives of probands with proliferative retinopathy was significantly higher compared with relatives of probands without proliferative retinopathy ($P = 0.0144$). Taking nephropathy into account did not substantially modify the relationship ($P = 0.0379$). The frequency of type 2 diabetes did not depend on the severity of the retinopathy in the probands when fathers

Table 3—*Insulin resistance components in first-degree relatives according to probands nephropathy stage*

	Probands diabetic nephropathy stage				
	Absent	Incipient	Established	Advanced	*P*
n (relatives)	306	126	74	72	
Sex (M/F)	139/167	62/64	35/39	32/40	0.8848
Age (years)	66 ± 11	66 ± 12	64 ± 13	65 ± 12	0.2632*
Personal history of type 2 diabetes (present/absent)	22/275	10/109	7/64	5/62	0.0001†
Personal history of hypertension (present/absent)	99/195	46/75	31/37	25/41	0.0655†
Personal history of dyslipidemia (present/absent)	87/204	42/74	30/38	22/37	0.0070†
Obesity status (NW/OW/Ob)	133/108/52	56/49/20	27/25/19	24/29/18	0.0001†
Insulin resistance score	0.31 ± 0.25	0.33 ± 0.26	0.39 ± 0.27	0.35 ± 0.25	0.04‡
n (fathers)	123	58	26	26	
Personal history of type 2 diabetes (present/absent)	13/111	4/51	3/24	4/22	0.5793§
Personal history of hypertension (present/absent)	47/77	22/34	13/13	12/13	0.1201§
Personal history of dyslipidemia (present/absent)	38/85	19/35	13/14	7/15	0.3469§
Obesity status (NW/OW/Ob)	46/50/27	21/29/8	8/9/9	7/14/5	0.4029§
Insulin resistance score	0.37 ± 0.26	0.33 ± 0.25	0.45 ± 0.27	0.37 ± 0.22	0.2907*
n (mothers)	134	61	31	32	
Personal history of type 2 diabetes (present/absent)	6/136	6/53	3/27	1/30	0.6131§
Personal history of hypertension (present/absent)	49/99	24/36	15/14	12/19	0.2211§
Personal history of dyslipidemia (present/absent)	45/92	22/35	15/15	13/17	0.0062§
Obesity status (NW/OW/Ob)	67/45/23	30/19/12	12/12/7	9/11/12	0.0077§
Insulin resistance score	0.29 ± 0.24	0.36 ± 0.26	0.43 ± 0.26	0.38 ± 0.27	0.0204*

Data are means ± SD or median (range). *ANOVA, †PROC GENMOD analysis, ‡PROC MIXED analysis, §χ^2 for trend test. Obesity status: NW, normal weight (BMI <25 kg/m^2)/OW, overweight (BMI 25–29.9 kg/m^2)/Ob, obese (BMI ≥30 kg/m^2).

Table 4—*Insulin resistance components in first-degree relatives according to probands retinopathy stage*

	Probands diabetic retinopathy stage			
	Stage 1	Stage 2	Stage 3	*P*
n (relatives)	246	114	218	
Sex (M/F)	111/135	55/59	102/116	0.8476
Age (years)	66 ± 12	66 ± 12	66 ± 12	0.8778*
Personal history of type 2 diabetes (present/absent)	20/214	5/107	19/189	<0.0001†
Personal history of hypertension (present/absent)	78/156	37/73	86/119	0.0002†
Personal history of dyslipidemia (present/absent)	69/161	42/67	70/125	0.0001†
Obesity status (NW/OW/Ob)	112/84/39	45/46/21	83/81/49	<0.0001†
Insulin resistance score	0.31 ± 0.25	0.31 ± 0.26	0.37 ± 0.25	0.06‡
n (fathers)	97	48	88	
Personal history of type 2 diabetes (present/absent)	12/84	3/46	9/78	0.6159§
Personal history of hypertension (present/absent)	35/60	20/29	39/49	0.2743§
Personal history of dyslipidemia (present/absent)	34/62	18/30	26/56	0.6174§
Obesity status (NW/OW/Ob)	38/39/20	16/23/9	28/40/20	0.3832§
Insulin resistance score	0.38 ± 0.26	0.34 ± 0.27	0.38 ± 0.25	0.6834*
n (mothers)	106	53	99	
Personal history of type 2 diabetes (present/absent)	6/104	1/52	9/90	0.2892§
Personal history of hypertension (present/absent)	39/72	16/36	45/52	0.1047§
Personal history of dyslipidemia (present/absent)	32/75	21/30	42/54	0.0408§
Obesity status (NW/OW/Ob)	55/34/17	23/19/11	40/34/26	0.0433§
Insulin resistance score	0.29 ± 0.23	0.32 ± 0.26	0.39 ± 0.26	0.0084*

Data are means ± SD or median (range). *ANOVA, †PROC GENMOD analysis, ‡PROC MIXED analysis, §χ^2 for trend test. Obesity status: NW, normal weight (BMI <25 kg/m^2)/OW, overweight (BMI 25–29.9 kg/m^2)/Ob, obese (BMI ≥30 kg/m^2).

and mothers were analyzed separately. However, the frequencies of obesity and hypertension in the relatives increased significantly with the severity of diabetic retinopathy in the probands. Systolic blood pressure was not related to the severity of retinopathy in the probands even when considering mothers or fathers separately (data not shown).

CONCLUSIONS — In this large family-based study, we found that the insulin resistance score was higher in first-degree relatives of probands with rather than without nephropathy. Interestingly, it was also higher in first-degree relatives of probands with severe retinopathy, even after controlling for nephropathy. We found that arterial hypertension and obesity segregated with retinopathy, whereas lipid disorders and obesity segregated with nephropathy. These results were particularly relevant in mothers of type 1 probands.

This study does, however, have some limitations. Hypertension in relatives was diagnosed by using a questionnaire and by recording blood pressure on just one occasion. Furthermore, we did not measure serum lipids; instead, we used a structured questionnaire to interview relatives. Moreover, we were not able to measure insulin resistance with the reference euglycemic clamp technique due to a very large number of relatives. We were also unfortunately not able to consider waist and hip circumferences. However, we found that insulin resistance was positively correlated with fasting insulinemia, HOMA-IR, and HbA_{1c}, strongly suggesting that this score effectively reflects insulin resistance, as recently suggested (35). A relationship was also found between the insulin resistance score and UAE, as proposed in the WHO working definition (16) and as shown in Finnish patients (36).

The characteristics of our study population were in good accordance with previous studies. In probands, blood pressure significantly increased with the severity of nephropathy (29). Diabetes duration was a major risk factor for severe diabetic retinopathy (37,38). The prevalence of hypertension, lipid disorders, and type 2 diabetes in relatives was in good accordance with data from the French general population (39,40). The sample frequency of case and control probands is very similar to what was expected from the general population (36).

We found that insulin resistance was higher in relatives of proband case subjects with nephropathy than in those of control subjects without nephropathy. This is in good accordance with three previous studies (26–28) showing that relatives of microalbuminuric or nephropathic patients are more resistant to insulin than relatives of normoalbuminuric patients, using the euglycemic clamp reference or other surrogate methods.

Our results extend our knowledge, showing that familial insulin resistance, in addition to nephropathy, is also related to retinopathy. This relationship between familial insulin resistance and the presence of microvascular complications in index type 1 diabetic subjects is in good accordance with the data from prospective follow-up studies (24,25), showing that insulin resistance is a risk factor for progression or development of retinopathy or nephropathy in type 1 diabetic patients. This report is the first to demonstrate an association between familial insulin resistance and the severity of retinopathy in diabetic first-degree relatives.

Our data support the hypothesis that insulin resistance has a familial component that affects the risk of microvascular disease. This is in good accordance with

the results from studies showing an increased risk of microangiopathy in diabetic patients that carry the genetic variants associated with insulin resistance in peroxisome proliferator–activated receptor-γ (41) or human glycoprotein PC-1 genes (42). However, insulin resistance syndrome is an intermediate phenotype with both genetic and environmental components. We therefore cannot infer from our data that the genetic components of risk for microangiopathy in type 1 diabetic subjects are due to the genetic components of insulin resistance. Instead, we can conclude that discrete components of the insulin resistance syndrome segregate with discrete manifestations of diabetic microangiopathy.

We evidenced an association between history of hypertension in relatives and diabetic nephropathy, as shown in some (8,9) but not all (43) previous reports. We found that mothers of nephropathic probands had higher SBP values than mothers of control subjects. This discrepancy for fathers may be related to the insufficient sensitivity of the office blood pressure measurement apparatus, as suggested by a Finnish study (10). Consistent with the possibility, the relatives of probands with nephropathy (incipient to advanced) displayed higher UAE than those of control subjects. Some candidate genes could explain the association between familial hypertension and retinopathy, such as endothelial nitric oxide synthase (44).

Personal history of dyslipidemia was slightly more frequent among relatives of index case subjects than others. This report confirms the data from a single-center family-based study showing a clustering of dyslipidemia with nephropathy (28). Familial clustering of lipid disturbances may partly account for the reported familial clustering of cardiovascular disease in type 1 diabetic patients with nephropathy (6,7,28,45). Lipid disturbances are well known to be associated with diabetic nephropathy (46,47), and prospective studies of type 1 diabetic patients have shown that an adverse lipid profile is predictive of the worsening of renal disease (18,48) or the least regression from microalbuminuria to normoalbuminuria (49). The adverse role of plasma lipids was recently found regarding renal and retinal complications in a longitudinal study (50). Several candidate genes involved in lipid metabolism could account for the relationship between familial lipid disorders and nephropathy, with apolipoprotein E being already widely studied (47,51,52).

Obesity in relatives was strongly associated with the risk of both severe retinopathy and nephropathy. This is in good accordance with previous reports showing that BMI was higher in type 1 diabetic patients who developed retinopathy (21) or nephropathy (24). Interestingly, the role of obesity in patients is not due to a familial resemblance, as BMI did not differ according to nephropathy or retinopathy stage of the index patients. Candidate genes for obesity are currently extensively studied, and some of them, such as adiponectin (53), could be associated with microvascular complications, as suggested by our results.

In conclusion, first-degree relatives are more insulin resistant when type 1 diabetic probands have more severe diabetic retinopathy or nephropathy. The components of the insulin resistance syndrome support the search for genetic factors involved in arterial hypertension and obesity for retinopathy and in lipids and obesity for nephropathy.

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APPENDIX

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