

Familial and Perinatal Risk Factors for Micro- and Macroalbuminuria in Young IDDM Patients

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It has been suggested that hereditary risk for hypertension and cardiovascular disease (CVD) as well as intrauterine growth may be involved in the pathogenesis of diabetic nephropathy. In the present study, we investigated the influence of familial and perinatal risk factors on the occurrence of micro- and macroalbuminuria in young IDDM patients. A cohort of 1,150 young patients with 5 years' duration of IDDM was screened for microalbuminuria. Data on family history of hypertension, CVD, IDDM, and NIDDM; perinatal factors such as birth weight, gestational age, and duration of breastfeeding; and maternal education, smoking, hypertension, and proteinuria during pregnancy were collected. We identified 75 patients with an albumin excretion rate $15 \mu\text{g}/\text{min}$ in more than two overnight urinary samples and compared them in a nested case-control study with three normoalbuminuric control subjects per patient from the same cohort, matched for diabetes duration. Perinatal factors were analyzed in all patients born at term (± 2 weeks), 59 of the 75 patients and 155 of the 225 control subjects. In univariate analysis, hypertension in parents (odds ratio [OR] 4.21), CVD in parents and grandparents (OR 1.26), maternal smoking during pregnancy (OR 3.21), and a low level of maternal education (OR 2.33) were significantly associated with the development of micro- and macroalbuminuria. When adjusted for other familial and perinatal factors, current mean blood pressure, HbA_{1c} , smoking, BMI, sex, age, and post-pubertal diabetes duration, using logistic regression analyses, only parental hypertension in all patients and maternal smoking during pregnancy and low level of maternal education in full-term patients were independent risk factors. When patients with poor glycemic control were analyzed separately, familial CVD, poor metabolic control, parental hypertension, maternal smoking during pregnancy, and level of maternal education were independent risk factors, with the adjusted OR markedly increased, compared with the matched subgroup with better HbA_{1c} . In conclusion, familial hypertension and CVD, maternal smoking during pregnancy, and low level of maternal education may independently increase the risk for incipient nephropathy in full-term offspring who later develop IDDM. Current poor glycemic control seemed to increase the effect of these risk factors. *Diabetes* 47:1121-1126, 1998

It is unknown why only 10–30% of IDDM patients are affected by diabetic nephropathy (1,2). Exposure to hyperglycemia seems to be a necessary but not sufficient risk factor for the development of nephropathy (3,4). Thus other susceptibility factors are likely to interact with the diabetic milieu in this process.

There is evidence of familial clustering of diabetic nephropathy (5,6). Parental hypertension is overrepresented among IDDM patients with overt proteinuria (7). Elevated blood pressure is already found during microalbuminuria (i.e., when renal function is still well preserved and thus unlikely to cause secondary hypertension) (8). This suggests that a genetic trait for hypertension may be involved in the pathogenesis of nephropathy. The relative mortality from cardiovascular disease (CVD) is markedly increased in patients with diabetic nephropathy (9); the presence of well-known cardiovascular risk factors (e.g., smoking, high cholesterol level, hypertension) alone cannot account for this association (10). A familial predisposition for this association has therefore been suspected (11), but also called in question (17).

Epidemiological studies have found fetal growth retardation to be associated with insulin resistance, hypertension, and CVD in adult life (13–15), all features of diabetic nephropathy. Whether intrauterine growth retardation gives rise to hypertension or CVD in adulthood, independent of familial predisposition for these conditions, is unknown. Little is known about the relationship between factors operating in utero or in early infancy and the later development of diabetic nephropathy. The possibility of an association between perinatal factors and diabetic renal disease, irrespective of hereditary risk factors for hypertension or CVD, has not previously been studied.

Having a deficient number of nephrons at birth has been implicated in the pathogenesis of postnatal development of glomerulosclerosis (16). According to one hypothesis, initially put forward by Brenner et al. (17), the formation of fewer nephrons, seen in low-birth-weight infants, may initiate systemic and glomerular hypertension and thus promote diabetic glomerulopathy. Rossing et al. (18) compared the risk for nephropathy between IDDM subjects with a low birth weight and those with a high birth weight. They found low birth weight to be associated with increased prevalence of nephropathy in women but not in men, but other possibly confounding perinatal risk factors were not taken into account. Several maternal factors are of importance for the etiology of intrauterine growth retardation: smoking, low social class, low level of education, malnutrition or protein deprivation, preeclampsia, hypertension, and/or renal disease (19). Whether these maternal conditions may be involved in the eti-

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AER, albumin excretion rate; CVD, cardiovascular disease; OR, odds ratio.

ology of nephropathy in offspring who also develop IDDM is unknown. However, because smoking enhances the risk for onset as well as progression of proteinuria in IDDM patients (20,21), it may be hypothesized that exposure to nicotine in utero may adversely affect renal function in postnatal life when coupled with diabetes.

In the present nested case-control study, we investigated the influence of putative familial and perinatal risk determinants: familial hypertension, CVD, NIDDM, and IDDM; intrauterine growth retardation; maternal education, smoking, hypertension, and proteinuria during pregnancy; and short duration of breast-feeding on the occurrence of micro- and macroalbuminuria in young IDDM patients.

RESEARCH DESIGN AND METHODS

Study population and procedure. The study was approved by the Ethics Committee of the Karolinska Institute and the Swedish Data Inspection Board. In Sweden, all children and adolescents ages 0–14 years with IDDM are referred to pediatric departments. To recruit a large sample of IDDM patients, we used the nationwide Swedish Childhood Diabetes Registry (22). Children registered between 7 January 1977 and 12 December 1987 were invited to participate in the present study. All children and adolescents with diabetes duration ≥ 5 years as of 1 January 1993 ($n = 3,858$) were contacted and sent an introductory letter with a brief description of the aim and scope of the study. Responses were obtained from 1,150 patients. Those who did not respond did not differ from those who did with regard to sex distribution, but were slightly older (20.3 ± 4.5 vs. 17.9 ± 4.9 years) and had a slightly longer duration of diabetes (10.9 ± 3.0 vs. 10.2 ± 3.0 years). The participants were asked to answer a questionnaire together with their parents concerning perinatal factors such as birth weight; gestational age (i.e., born at term, >2 weeks early, or >2 weeks late); maternal smoking, hypertension, or proteinuria during pregnancy; duration of breast-feeding; and maternal age and level of education. The family history of morbidity or death related to CVD, hypertension, IDDM, NIDDM, and diabetic nephropathy was also collected from the questionnaire, together with the parents' and grandparents' age at the time of the study or their age at death. Information on patients' current smoking habit (i.e., number of cigarettes/day [1–5, 6–10, or >10 /day]) was also gathered. Data on patients' current HbA_{1c} and blood pressure (± 3 months), occurrence of simplex or proliferative retinopathy, insulin dosage, weight, and height were obtained from medical records. Laboratory methods of HbA_{1c} differ throughout the country, but the mean coefficient of variation between the methods used during the year of this study was estimated at 7% (EQUALIS Reference Laboratory, unpublished data); however, the method used was the same within each of the 24 counties and within most of the six regions. The distribution of study and control subjects was similar over the 24 counties, as determined by the Mann-Whitney *U* test ($P = 0.63$), and did not differ within regions, as determined by χ^2 tests. Regional data were always adjusted for in the multivariate analyses. Thus a systematic bias as to case control status was improbable.

All subjects were carefully instructed and asked to deliver by mail two timed overnight urine samples to the Department of Clinical Chemistry at Norrlands University Hospital in Umeå for analysis of albumin excretion rate (AER) by an immunoturbidimetric method (23) using an automated spectrophotometer (Hitachi 911, Tokyo, Japan). Intra- and interassay coefficients of variation were 2.40 and 5.84%, respectively. Microalbuminuria was considered to be present if AER was 15–200 $\mu\text{g}/\text{min}$ in both samples, and macroalbuminuria if AER was > 200 $\mu\text{g}/\text{min}$. If only one urinary test screened positive, the patient was asked for a third sample. Thus, the definition of micro- or macroalbuminuria was based on at least two out of three urinary tests.

A nested case control study was designed based on the cohort of 1,150 patients. Of these, 75 patients with micro- ($n = 69$) or macroalbuminuria ($n = 6$) were followed; 3 control subjects per patient ($n = 225$), matched only for diabetes duration, were randomly chosen from the remaining 1,075 normoalbuminuric subjects in the cohort. The female/male ratio, current age, BMI, and blood pressure level were higher among the patients than among the control subjects. Postpubertal diabetes duration (defined as duration after age 12 years in girls and after age 14 years in boys) was longer among the patients ($P = 0.04$). HbA_{1c} was not significantly different between the groups. Clinical data on all study participants are presented in Table 1.

Because the exact gestational age was not obtained from the questionnaire, only those of the 300 participants reported to be born at term (± 2 weeks) were included when analyzing the relative risks of perinatal risk factors. Therefore, in these analyses the matching was resolved, but total duration of IDDM was similar between groups. Postpubertal duration tended to be longer among the patients ($P = 0.08$). The information obtained on birth weight and gestational age (term ± 2 weeks) was validated by comparison with data from the Swedish Medical Birth Registry, available for patients born after 1973 (38 patients and 137 control subjects). Among the 175 patients validated in the Registry, the sensitivity for having a birth weight $<2,500$ g, and the specificity for having a birth weight $>2,500$ g were each 100%. Only one patient with microalbuminuria was misclassified regarding gestational age, leading to this patient being excluded from statistical analysis. Clinical data on the subgroup of 59 patients and 155 control subjects included in the subanalyses of perinatal risk factors are presented in Table 2.

Statistical analysis. Comparisons of means between groups were performed by the unpaired Student's *t* test. Distributions of sex, retinopathy, and hypertensive treatment were analyzed by the Kolmogorov-Smirnov two-sample test.

Univariate and multivariate analyses were performed using the Quest Epidemiological and Statistical Program (L. Gustavsson, University of Umeå, Sweden) and the Statistical Package for Social Science (SPSS, Chicago). In the univariate analysis, the crude odds ratios (ORs) were calculated. A positive family history of CVD was specified as myocardial infarction, brain infarction (thrombotic or hemorrhagic), or death related to these diagnoses. Hypertension was defined as high blood pressure treated with antihypertensive medication. Variables, including perinatal risk factors, were dichotomized using the exposed levels as follows: birth weight $<2,500$ g, smoking during pregnancy (yes/no), breast-feeding <3 months, treated or untreated hypertension during pregnancy, dipstick positive proteinuria during pregnancy, and maternal education below high school level.

In the logistic regression analyses, all variables except for age, postpubertal duration of diabetes, HbA_{1c}, region (as a categorical variable), and BMI were

TABLE 1
Clinical characteristics of all study participants

	Patients	Control subjects	<i>P</i> value
<i>n</i>	75	225	
Sex (M/W)	31/44	127/98	0.02
Age (years)	20.2 \pm 4.0	18.7 \pm 5.1	0.01
Age at onset of IDDM (years)	9.1 \pm 3.0	7.6 \pm 3.9	0.01
Duration of IDDM (years)	11.1 \pm 2.9	11.1 \pm 2.9	—
Insulin dosage (U/kg)	0.98 \pm 0.28	0.96 \pm 0.26	0.57
HbA _{1c} (%)	8.2 \pm 2.3	7.6 \pm 1.6	0.21
Systolic blood pressure (mmHg)	125 \pm 10	117 \pm 10	<0.001
Diastolic blood pressure (mmHg)	78 \pm 8	73 \pm 8	<0.001
BMI (kg/m ²)	23.5 \pm 2.7	22.0 \pm 2.9	<0.001
Retinopathy (yes/no)	16/56	36/167	0.4

Data are means \pm SD or *n*.

TABLE 2
Clinical characteristics of patients born at term

	Patients	Control subjects	<i>P</i> value
<i>n</i>	59	155	
Sex (M/W)	23/36	84/71	0.31
Age (years)	20.3 \pm 4.2	19.0 \pm 5.1	0.06
Age at onset of IDDM (years)	9.1 \pm 2.9	7.8 \pm 3.9	0.02
Duration of IDDM (years)	11.2 \pm 3.1	11.1 \pm 3.0	0.79
Insulin dosage (U/kg)	1.04 \pm 0.19	1.02 \pm 0.12	0.41
HbA _{1c} (%)	8.4 \pm 1.8	7.9 \pm 1.6	0.06
Systolic blood pressure (mmHg)	125 \pm 11	116 \pm 10	<0.001
Diastolic blood pressure (mmHg)	76 \pm 7	73 \pm 8	0.01
BMI (kg/m ²)	23.3 \pm 2.8	22.3 \pm 2.9	0.02
Retinopathy (yes/no)	18/41	19/136	0.09

Data are means \pm SD or *n*.

dichotomous. For analysis of familial hypertension as a risk factor, only data from parents were used, since hypertension among grandparents might be due to different causes other than the genetic trait in which we were interested. Familial CVD as a risk factor was reported in both parents and grandparents due to the young age of patients and their parents. All variables were forced into the regression, and the independent significance of an estimated coefficient of a variable was tested using the Wald statistic. To analyze possible interactions between metabolic control on the one hand and familial and perinatal risk factors on the other, the relative influence of these risk factors was analyzed in two subgroups determined by whether the subjects' current HbA_{1c} was below or above the median value (8%) for the whole study population.

RESULTS

Familial risk factors. Age at study or age at death in parents and grandparents did not differ between patients and control subjects (data not shown). CVD in parents and grandparents was associated with significant risk increases for micro- and macroalbuminuria in probands, as was parental hypertension, whereas familial IDDM and NIDDM were not (Table 3). Too few subjects with diabetic nephropathy among siblings ($n = 1$), parents ($n = 4$), and grandparents ($n = 6$) were traced to assess any possible associations.

When modeling the risk for nephropathy as a function of familial CVD, hypertension, IDDM, and NIDDM, familial CVD and hypertension were both significant, independent risk factors (OR = 1.23, $P = 0.03$ and OR = 3.97, $P = 0.001$, respectively). We also modeled the risk for micro- and macroalbuminuria as a function of familial risk factors (hypertension, CVD, IDDM, and NIDDM) and adjusted the data for the following individual potential confounders: age, sex, BMI, post-

pubertal duration, mean arterial blood pressure, current HbA_{1c}, region, and cigarette smoking. In this model, only parental hypertension remained independent (Table 4).

Perinatal risk factors among those born at full term. Mean weight and height at birth and ponderal index were similar between the 59 patients and the 155 control subjects born at term. Birth weight was $3,573 \pm 583$ vs. $3,614 \pm 465$ g, birth height was 50.5 ± 2.8 vs. 50.6 ± 2.4 cm, and the ponderal index was 0.0279 ± 0.0027 vs. 0.0277 ± 0.0033 g/cm³ in patients and control subjects, respectively.

Maternal smoking during pregnancy and low level of maternal education were associated with a significant increased risk for later micro- and macroalbuminuria. A short breast-feeding period and low birth weight were marginally significant, whereas low birth weight and maternal hypertension or proteinuria during pregnancy did not significantly affect the risk for microalbuminuria in the offspring. Crude ORs are presented in Table 5. Parental hypertension was associated with micro- and macroalbuminuria (OR 3.64, $P = 0.002$), as was familial CVD (OR 1.31, $P = 0.01$). No other familial risk variables were significantly associated with the occurrence of micro- and macroalbuminuria among these patients. Current smoking tended to be associated with micro- and macroalbuminuria (OR 2.47 [0.93–6.57], $P = 0.07$). The only independent risk determinants for having micro- and macroalbuminuria in this subgroup, when taking all individual and familial confounders listed above into account, were maternal smoking during pregnancy and a low level of maternal education (Table 6).

When the relative influence of maternal smoking during pregnancy, maternal level of education, parental hypertension, and familial CVD in patients with HbA_{1c} above or below the median for all patients was analyzed separately, adjusted ORs for these variables were significantly increased only among patients with poor metabolic control, indicating a positive interaction for these factors with poor metabolic control (Table 7).

TABLE 3
Familial CVD, hypertension, IDDM, and NIDDM, and risk for incipient nephropathy (univariate analysis)

	Patients	Control subjects	Crude OR	<i>P</i> value
<i>n</i>	75	225		
Familial CVD				
Siblings	0	0	—	—
Parents	6	6	3.32	0.05
Grandparents	124	273	1.24	0.02
Parents and/or grandparents	130	279	1.26	0.01
Familial hypertension				
Siblings	0	2	—	—
Parents	22	19	4.21	0.0000
Grandparents	44	154	0.85	0.36
Parents and/or grandparents	66	173	1.14	0.35
Familial IDDM				
Siblings	7	19	1.05	0.91
Parents	9	23	1.20	0.67
Grandparents	15	40	1.12	0.70
Parents and/or grandparents	24	63	1.13	0.59
Familial NIDDM				
Siblings	0	0	—	—
Parents	3	3	3.08	0.17
Grandparents	22	57	1.15	0.57
Parents and/or grandparents	25	60	1.23	0.37

Data are *n*.

DISCUSSION

The major finding of this nested case control study was that familial hypertension, familial CVD, low level of maternal education, and maternal smoking during pregnancy, in the presence of poor metabolic control, seemed to increase,

TABLE 4
Adjusted ORs from the logistic regression analysis including significant familial risk factors from the univariate analysis and other potential individual confounders

Variable	OR	<i>P</i> value
Parental hypertension	2.68	0.03
Familial CVD	1.18	0.12
Age	0.93	0.79
Sex	1.49	0.44
BMI	1.08	0.28
Postpubertal duration of IDDM	1.08	0.79
Current HbA _{1c}	1.17	0.07
Region	0.81	0.04
Mean blood pressure	1.08	0.0008
Current smoking	1.42	0.53

TABLE 5
Crude ORs for having micro- and macroalbuminuria by prenatal risk factors

	Category		Numbers exposed			
	Exposed	Unexposed	Patients	Control subjects	OR	P value
Birth weight	<2,500 g	2,500 g	5	5	2.77	0.07
Maternal smoking during pregnancy	yes (any smoking)	no	15	15	3.21	0.02
Maternal education	<high school	high school	43	83	2.33	0.01
Breast-feeding	<3 months	3 months	24	42	1.92	0.05
Maternal hypertension during pregnancy	yes (treated or untreated)	no	4	7	1.62	0.46
Maternal proteinuria during pregnancy	dipstick positive	dipstick negative	4	10	1.17	0.79

independently of each other, the risk for micro- and macroalbuminuria in the offspring who later developed IDDM.

The finding that parental hypertension and familial CVD were risk factors independent of each other leads to the speculation that different genetic predispositions for these conditions may be operating in the determination of susceptibility for diabetic nephropathy. The influence of parental hypertension found in our study agrees with the findings of some but not all (24) previous studies showing either higher mean blood pressure levels (7) or increased prevalence of reported hypertension (11,25) among nondiabetic parents of IDDM probands with albuminuria compared with those of IDDM patients with normoalbuminuria. However, we also showed that current poor metabolic control increased the OR for having microalbuminuria in patients with parental hypertension, indicating an interaction between heredity for hypertension and hyperglycemia. This is compatible with a recent report that carriers of the C¹¹⁶⁶ allele of the ANG II type 1 receptor gene (a gene possibly involved in blood pressure regulation) only in the presence of hyperglycemia markedly increases the risk for diabetic nephropathy (26). It is possi-

ble that other candidate genes involved in the renin-angiotensin system or genes determining sodium/lithium counter transport are responsible for the association between familial hypertension and diabetic nephropathy (4).

Proteinuria is a strong predictor of death from CVD and the development of coronary artery disease (9). In a study by Earle et al. (27), a significant excess of CVD was found among parents of IDDM patients with proteinuria when compared with parents of IDDM patients who did not develop kidney disease. However, in contrast to our study, the effect of familial CVD was not adjusted for when considering the effect of hypertension (27). Our finding of independent effects of familial hypertension and familial CVD suggests that these risk factors exert their influences through different mechanisms. However, hyperglycemia seems to be a prerequisite for the deleterious effect of familial CVD. The influence of familial CVD may be partly due to shared environment. Still, in the general population, simple familial clustering of environmental factors does not account entirely for the familial aggregation of CVD, suggesting that genetic factors are also important (28). The insertion/deletion polymorphism of the ACE gene has been much discussed in this context (29–31). The indications of an association between this genotype and diabetic nephropathy have also been controversial (32–35). Whether the increased risk for microalbuminuria in patients having a familial predisposition to CVD is related to ACE-gene polymorphism is currently under investigation in our department. In contrast to our findings, Norgaard et al. (12) did not find a familial predisposition to CVD in IDDM patients with nephropathy, probably due to the

TABLE 6
Adjusted ORs from the logistic regression analysis, including identified significant risk determinants in the univariate analysis and potential other familial and individual confounders

Variable	OR	P value
Maternal smoking during pregnancy	3.08	0.04
Maternal education	2.85	0.04
Breast-feeding	2.52	0.08
Birth weight	1.53	0.66
Maternal hypertension during pregnancy	0.88	0.93
Maternal proteinuria during pregnancy	0.39	0.42
Current age	0.60	0.21
Sex	2.18	0.34
Postpubertal diabetes duration	1.65	0.24
Current HbA _{1c}	1.06	0.60
Region	0.81	0.21
Mean blood pressure	1.07	0.10
Current smoking	3.96	0.15
BMI	1.16	0.13
Parental hypertension	2.16	0.25
Familial CVD	1.23	0.23

TABLE 7
Logistic regression analysis of micro- and macroalbuminuria as a function of maternal smoking during pregnancy, maternal education, parental hypertension, and familial CVD in 214 patients born at term

Variable	Patients with HbA _{1c} median		Patients with HbA _{1c} <median	
	OR	P value	OR	P value
Maternal smoking during pregnancy	3.69	0.035	1.24	0.86
Maternal education	8.93	0.006	1.94	0.16
Parental hypertension	6.56	0.065	1.67	0.42
Familial CVD	2.20	0.004	0.91	0.57

young parental age in that study. To avoid this problem, we included information from parents as well as grandparents to increase the number of potential CVD cases and thus the power of the study.

In the present study design, we matched patients and control subjects for diabetes duration only; this revealed a younger age at onset among normoalbuminuric compared with albuminuric patients, indicating that postpubertal duration could be a risk factor. No statistically significant effect of postpubertal duration was found, but age, sex and postpubertal age were adjusted for in all multivariate analyses.

Familial NIDDM among parents or grandparents was not proven to be a risk factor for micro- or macroalbuminuria in our study. Increased insulin resistance among parents of microalbuminuric IDDM patients has previously been reported (36). However, the collected information on NIDDM from the mailed questionnaires might have diluted the association and thus increased the risk for a type II error in our study.

It is well known that maternal tobacco use is the most powerful determinant of poor fetal growth in Western countries, and may reduce birth weight 250 g in full-term babies (37). Such an association was also seen in our study, where an inverse correlation between smoking during pregnancy and birth weight was found (data not shown). Thus, because intrauterine growth retardation may lead to increased intraglomerular and systemic blood pressure, which in turn may promote the development of diabetic renal disease, low birth weight and elevated blood pressure not only may be confounders but also may be intermediate variables in the causal pathway between maternal smoking during pregnancy and incipient nephropathy in the offspring. Introduction of putative intermediate variables in the logistic regression analysis could potentially bias the estimated effect of maternal smoking. However, in the multivariate analysis, maternal smoking during pregnancy was a significant risk factor independent of low birth weight or blood pressure levels in the full-term offspring who later developed IDDM. Thus it is less likely that the suggested effect of smoking during gestation relates only indirectly to the development of incipient nephropathy through putative intermediate risk factors. Although low birth weight tended to increase the OR for having microalbuminuria in the univariate analysis, it was not independent of the potential confounders in the multivariate analysis; the lack of influence of low birth weight should be interpreted with some caution due to the small numbers; however, our findings do indicate that low birth weight may be a confounding factor. The same could be true for the study by Rossing et al. (18), who found that birth weight <10th percentile versus birth weight >90th percentile was associated with increased prevalence of diabetic nephropathy in adult IDDM women but not men, but those investigators did not take into account maternal smoking and other perinatal risk factors.

In agreement with a previous report on adolescents (38), we found that current smoking tended to be related to microalbuminuria. Smoking habits may be socially inherited. However, in the present study, no association between maternal smoking during pregnancy and current smoking of the patient was seen, and maternal smoking during gestation was a risk factor independent of patients' smoking habits. The mechanism by which intrauterine exposure to nicotine may affect postnatal renal function is so far unknown. However,

maternal smoking gives rise to increased fetal carboxyhemoglobin and reduced placental blood flow that leads to a low oxygenation of the fetal tissue (37). It may be that circulatory changes promoting high pressure in the fetal circulation to maintain placental perfusion result in adaptive changes in the fetus leading to an increased risk for systemic as well as glomerular hypertension followed by acquired glomerular sclerosis in IDDM patients.

Diabetic nephropathy was previously reported to be more prevalent among patients with a low socioeconomic status (39). A good indicator of socioeconomic status in families is the mother's level of education. In the present study we could confirm a relative importance of low maternal education for the risk of having microalbuminuria. Low education and low social class may be of major importance for the quality of glycemic control, which is a well-known determinant for the development of diabetic nephropathy. Interestingly, we found indications of a synergistic effect between poor metabolic control and a low level of maternal education. In addition, a low level of maternal education exerted its statistical effect independently of maternal smoking habits during pregnancy. Taken together, this suggests that other factors accompanying low social class (e.g., poor nutritional status with a low protein intake during gestation) may affect the risk for later microalbuminuria in the offspring, as indicated by experimental studies in rats (16).

The negative results regarding the influence of hypertension and proteinuria during pregnancy on the occurrence of microalbuminuria in offspring should be interpreted with some caution, as a nondifferential misclassification (i.e., similar between patients and control subjects) of exposure cannot be definitely excluded. Such a misclassification may cause a dilution of the relative risk.

The interpretation of patient-control subject data collected from questionnaires, as in our study, may have a disease-dependent bias. However, neither our patients nor their mothers knew the results of our urinary albumin excretion analysis or their allocation to the study or control group when answering the questionnaire, even though some of them might have been aware of previous positive microalbuminuria tests performed locally. It is furthermore unlikely that the patients were aware of the possibility that birth weight, smoking during pregnancy, or other perinatal factors were associated with nephropathy. Even if questionnaire data on certain exposure variables might have had low sensitivity or specificity as compared with hospital data, it should be emphasized that this would only make the ORs tend to approach unity (i.e., all ORs reported are very conservative estimates but never overestimates of risk).

Our study participants had a relatively short duration of diabetes, and some of the normoalbuminuric control subjects might develop microalbuminuria later. Thus it is important to note that our results are valid only in populations with a mean diabetes duration of 11 years and a mean age of 20 years; our findings must be confirmed in patients with longer diabetes duration. On the other hand, the low occurrence of microalbuminuria in our study (6.5%) agrees with results from a recent prospective study in Sweden in which only 5.8% of young patients with onset of IDDM between 1971 and 1975 developed nephropathy within 20 years of follow-up (2).

Although our study does not give a full assessment of risk factors for diabetic nephropathy, it suggests for the first time

that parental hypertension, familial CVD, and maternal smoking during pregnancy together with a low maternal level of education may independently of each other, but in interaction with hyperglycemia, enhance the risk for renal affection in full-term offspring who later develop IDDM. These findings may contribute to new hypotheses about the complex mechanism of development of diabetic nephropathy where familial, perinatal, as well as environmental factors may all be operating.

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