Predictors of Progression From Normoalbuminuria to Microalbuminuria in NIDDM

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OBJECTIVE — Our objective was to establish the clinical, genetic, metabolic, and immunologic risk factors for the progression of the albumin excretion rate (AER) in normoalbuminuric NIDDM patients.

RESEARCH DESIGN AND METHODS — We recruited 108 NIDDM patients with normal AER after a diabetes duration of 9 years to participate in a prospective 9-year follow-up. In addition to conventional clinical and metabolic variables, we assessed microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary heart disease, peripheral vascular disease) diabetic complications, genetic markers (HLA genotypes), and organ-specific autoimmune markers, including islet cell antibodies. Multiple logistic regression was used to determine independent predictors of progression of AER.

RESULTS — A total of 21 patients (19%) died during the follow-up. There was an overrepresentation of men (61 vs. 39%; $P = 0.044$) and smokers (55 vs. 27%; $P = 0.01$) in patients who progressed to micro- or macroalbuminuria versus those who did not progress. In addition, progressors had higher fasting plasma glucose ($P = 0.002$) and HbA_1 ($P = 0.0002$) concentrations at baseline than did nonprogressors. Neuropathy was more often seen in progressors than in nonprogressors at baseline (53 vs. 16%; $P = 0.0004$). Frequency of HLA genotypes and autoimmune markers did not differ between progressors and nonprogressors. In a multiple logistic regression analysis, HbA_1 ($P = 0.0005$) and a history of smoking ($P = 0.011$) were independent predictors of progression of AER.

CONCLUSIONS — This study reemphasizes the importance of poor glycemic control and smoking as independent risk factors for progression of AER. Furthermore, development of micro- or macroalbuminuria in NIDDM was associated with neuropathy and male sex.

Diabetes Care 21:1932–1938, 1998

Microalbuminuria is a strong predictor of both diabetic nephropathy and cardiovascular disease in patients with IDDM and those with NIDDM (1–4). In contrast to IDDM patients (about 32%) (5), only about 3% of NIDDM patients die from end-stage renal disease (6). This is somewhat surprising in light of the high prevalence (10–30%) of microalbuminuria in European NIDDM patients (7–9). One explanation is that in NIDDM progression of albumin excretion rate (AER) predicts progression of macrovascular disease rather than progression of diabetic nephropathy. If this explanation is correct, AER progressors could be expected to already have more cardiovascular disease (CVD) at baseline but also to show progression of CVD during follow-up.

The cardiovascular risk seems to already increase at levels of albuminuria lower than those used to define microalbuminuria (10,11). In a study by Damsgaard et al. (12), nondiabetic subjects with AERs above the median of 7.5 μg/min had a threefold higher 7-year mortality rate compared with patients with AERs below the median (12). In a study of NIDDM patients, the risk of vascular death was increased already at AERs above 10 μg/min (13). In some previous studies, worse glycemic control, higher baseline AER, systolic blood pressure, age, cholesterol concentration, male sex, and the presence of retinopathy predicted the transition from normo- to microalbuminuria in NIDDM (9,14–17). None of these studies indicated that macrovascular disease predicted progression of AER. This could be at least partly explained by the relatively crude measurements available for the detection of macrovascular disease. In addition to clinical and metabolic risk factors, genetic predisposition is also believed to affect the incidence and outcome of diabetic complications (18,19). Therefore, the aim of this study was to assess the role of clinical, metabolic, genetic, and immunologic risk factors for the progression of AER and its relationship to the progression of micro- and macroangiopathy.

RESEARCH DESIGN AND METHODS

Patients

In an attempt to identify predictors of progression from normo- to microalbuminuria in NIDDM, we followed a cohort of 108 (52 men, 56 women) normoalbuminuric NIDDM patients for 9 years. The patients, aged between 35 and 70 years, were randomly selected from the register of the Helsinki Diabetes Association. NIDDM was

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Received for publication 3 February 1998 and accepted in revised form 15 June 1998.

Abbreviations: ABI, ankle/brachial ratio; AER, albumin excretion rate; CVD, cardiovascular disease; HOMA, homeostasis model assessment.

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

defined according to World Health Organization criteria (20). The patients were first studied in 1983–1985 and restudied in 1993–1995. All patients gave their informed consent, and the study protocol was approved by the local ethics committee.

Twenty-one patients (19%) died during the follow-up, and seven patients (6%) were lost. However, their medical records were in most cases (four patients) available, and information about their current status could therefore be obtained. Eighty (74%) of the original 108 patients participated in a complete follow-up visit at our clinic. In addition, data on the progression of albuminuria were available from 10 of the remaining patients. Therefore, the final analysis included data on 90 patients.

At baseline, all patients were assessed for microvascular disease (retinopathy, neuropathy, albuminuria), macrovascular disease (coronary heart disease, peripheral vascular disease), and the presence of genetic (HLA) and immunologic (islet cell antibody and other organ-specific antibodies) markers.

Fasting blood samples were drawn for the measurement of blood glucose, glycated hemoglobin (HbA_1), serum total and lipoprotein lipids, and creatinine concentrations. C-peptide and insulin concentrations were measured in serum samples taken before and 6 min after an intravenous injection of 1 mg of glucagon (21). Insulin resistance was calculated as fasting insulin $\times$ fasting glucose/22.5 using the homeostasis model assessment (HOMA) (22). Three 24-h urine collections were used for the measurement of AER and creatinine clearance. At follow-up, all measurements except the assessment of retinopathy and neuropathy were repeated. Instead of 24-h urine collections, overnight urine collections were used to measure the AER at follow-up.

Assessment of microangiopathy and macroangiopathy

Retinopathy was assessed by direct ophthalmoscopy and fluorescein angiography of the ocular fundi and considered present if a patient had $\geq$10 microaneurysms per eye in the fluorescein angiogram. In addition to a clinical neurological examination, peripheral neuropathy was evaluated with measurement of conduction velocities of peripheral nerves with an electroneuromyography device (DISA Elektronik A/S, Skovlunde, Denmark). If two different nerves showed pathological conduction velocities, the patient was considered to have neurophysiologically diagnosed peripheral neuropathy. The autonomic nervous system was tested by heart-rate variation at rest, during maximal 6/min deep breathing, and during the Valsalva maneuver, and by quantitating differences in heart rate and blood pressure between supine and postural positions. Microalbuminuria was defined as AER 30–300 mg/24 h or 20–200 µg/min (in overnight urine collections), and macroalbuminuria was defined as AER $>$300 mg/24 h or $>$200 µg/min in two of three urine collections.

Macroangiopathy was defined as the presence of coronary heart disease, peripheral vascular disease, and/or stroke. Electrocardiograms were recorded from each study subject and coded using the Minnesota coding by one investigator (K.J.T.). Coronary heart disease was defined as a medical history of myocardial infarction and/or the presence of probable myocardial infarction in the electrocardiogram (Minnesota codes 1.1-2), or as both treatment with long-acting nitroglycerin and presence of signs of possible myocardial ischemia in the electrocardiogram (Minnesota codes 1.3, 4.1-4, 5.1-3, 7.1) (23). Peripheral vascular disease was evaluated using a Doppler device to measure the blood pressure at ankle and arm level and calculating the ankle/brachial ratio (ABI) as described by Lepäntalo et al. (24). An ABI $<$0.85 was considered abnormal. Blood pressure was measured in the sitting position after a 15-min rest using a mercury sphygmomanometer. The mean value of three measurements taken in 5-min intervals was used for the analysis. Hypertension was defined as blood pressure $\geq$160/95 mmHg or treatment with antihypertensive drugs.

Analytical methods

Plasma glucose was assayed in duplicate by a hexokinase method (Boehringer Mannheim, Mannheim, Germany) at baseline and with a glucose oxidase method using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA) at follow-up. Glycohemoglobin (HbA_1) concentration in blood at baseline was measured by microcolumn chromatography (Isolab, Akron, OH) after overnight incubation of the samples in saline. The reference level for the assay was 5.0–7.0%. At follow-up, HbA_{1c} was determined by high-pressure liquid chromatography with a normal range of 4.0–6.0% (Diamat Analyzer; Biorad Laboratories, Germany). HbA_{1c} at follow-up was transformed to HbA_1 by multiplying by 1.33. Baseline serum insulin concentrations were measured in duplicate using antiserum M 8170, ^{125}I(tyr A 19)-labeled porcine insulin as tracer, and human monocomponent insulin as standard (Novo Research Institute, Bagsvaerd, Denmark) (25). Precipitation of the antigen-antibody complex was performed using an ethanol separation technique. The sensitivity of the assay was 0.005 nmol/l, and the interassay coefficient of variation was 11%. At follow-up, serum insulin concentration was determined with a double antibody radioimmunoassay (Pharmacia, Uppsala, Sweden) with an interassay coefficient of variation of 5%. C-peptide concentrations were determined in duplicate by radioimmunoassay (26). The sensitivity of the C-peptide assay was 0.01 nmol/l, and the interassay coefficient of variation was 9%. Lipoprotein fractions were separated according to Havel et al. (27) by sequential ultracentrifugation from blood samples taken after an overnight (12-h) fast, using a Ti 50 rotor in Sorvall OTD 65 preparative ultracentrifuge (DuPont Instruments, Wilmington, DE) (28). The concentrations of cholesterol and triglycerides in total plasma and the separate lipoprotein fractions at baseline were determined by enzymatic methods using commercial kits (kit no. 187313 for cholesterol and kit no. 297771 for triglyceride; Boehringer Mannheim). Serum free fatty acid was measured with a microfluorometric method (29). Serum and urine creatinine concentrations were analyzed with a kinetic method (normal range: women 50–110, men 55–115 µmol/l) (Kone Oy Reag, Espoo, Finland). Urinary AER was measured with radioimmunoassay (Pharmacia, Uppsala, Sweden) from three 24-h urine collections at baseline and with immunoturbidometry from three overnight urine collections at follow-up. The detection limit for the radioimmunoassay method was 2 mg/l, and the interassay coefficient of variation was 5%. The corresponding values for the immunoturbidimetric method were 5 mg/l and 7.5 ± 1%, respectively. Organ-specific antibodies (thyroid microsomal antibodies, thyroglobulin antibodies, islet cell antibodies, and gastric parietal antibodies) were determined as previously described (30). HLA typing was performed by a standard two-stage cytotoxicity method with a total of 120 antisera defining 11 A-locus, 20 B-locus, and 7 Cw-locus specificities. Eight DR specificities, DR1–DRw8, were determined with a minimum of 60 antisera.

Statistical analysis

All data are expressed as means ± SEM unless otherwise stated. Differences between group means were tested with analysis of variance or Mann-Whitney *U* test where appropriate. Pearson's χ^2 test or two-tailed Fisher's test was used to test frequency differences.

Comparisons between follow-up and baseline data were performed using Wilcoxon signed-rank test for continuous data and McNemar's test for categorical data. AER, creatinine clearance, and total triglyceride concentration were analyzed after $\log_e$ transformation because of skewed distributions. Independent predictors of progression of albuminuria were identified with a multiple logistic regression analysis. All data were analyzed using a BMDP statistical package (Biomedical Data Processing, version 7.0, 1992, Los Angeles, CA). A P value <0.05 was considered statistically significant.

RESULTS

Characteristics of progressors and nonprogressors at baseline

During the follow-up period, 31 patients (34%) progressed from normoalbuminuria to microalbuminuria (22 patients) and macroalbuminuria (9 patients). None of the patients developed end-stage renal disease during the study. Patients who progressed from normoalbuminuria to micro- or macroalbuminuria (progressors) had higher fasting plasma glucose ($P = 0.002$) and HbA_1 concentrations ($P = 0.0002$) than those who remained normoalbuminuric during the follow-up (nonprogressors). There were more men ($P = 0.044$) and current ($P = 0.035$) as well as former smokers ($P = 0.010$) among progressors than among nonprogressors. There was also a trend toward higher initial AER in the progressors versus nonprogressors ($P = 0.058$). No differences were observed in lipids, lipoproteins, or blood pressure between the two groups (Table 1). Neither was there any difference in the prevalence of macrovascular disease at baseline. Progressors had an increased prevalence of peripheral neuropathy ($P = 0.0004$), whereas no differences were observed in the variables measuring autonomic neuropathy (Table 2). Progressors did not differ from nonprogressors with respect to the frequency of different HLA-DR types or autoimmune markers (Table 3).

To further study the role of initial AER on progression of AER, we compared patients with AER above and below the median AER at baseline (2.5 mg/24 h). The progression of AER was more prevalent in patients with initial AER above than below the median (48 vs. 23%; $P = 0.019$).

Table 1—*Baseline clinical characteristics of normoalbuminuric NIDDM patients with and without progression to micro- or macroalbuminuria during the 9-year follow-up period*

	Progressors	Nonprogressors	*P* value
n (M/W)	31 (19/12)	59 (23/36)	0.044
Age (years)	58.1 ± 1.1	57.3 ± 0.8	—
Duration of diabetes (years)	10.5 ± 0.8	8.6 ± 0.6	—
Insulin treatment	26	19	—
BMI (kg/m^2)	26.8 ± 0.7	27.4 ± 0.5	—
Systolic blood pressure (mmHg)	152 ± 5	154 ± 3	—
Diastolic blood pressure (mmHg)	89 ± 2	87 ± 1	—
Fasting plasma glucose (mmol/l)	12.3 ± 0.6	9.9 ± 0.4	0.002
HbA_1 (%)	10.8 ± 0.3	9.3 ± 0.2	0.0002
Triglycerides (mmol/l)	2.44 ± 0.39	2.24 ± 0.29	—
VLDL triglycerides (mmol/l)	1.57 ± 0.31	1.34 ± 0.20	—
LDL triglycerides (mmol/l)	0.49 ± 0.04	0.55 ± 0.06	—
Cholesterol (mmol/l)	6.24 ± 0.36	6.26 ± 0.18	—
HDL cholesterol (mmol/l)	1.35 ± 0.07	1.41 ± 0.05	—
HDL_2 cholesterol (mmol/l)	0.71 ± 0.07	0.77 ± 0.05	—
HDL_3 cholesterol (mmol/l)	0.62 ± 0.03	0.63 ± 0.02	—
LDL cholesterol (mmol/l)	4.27 ± 0.23	4.22 ± 0.13	—
VLDL cholesterol (mmol/l)	0.75 ± 0.15	0.62 ± 0.11	—
Free fatty acid (mmol/l)	904 ± 65	868 ± 40	—
Fasting serum C-peptide (nmol/l)	0.48 ± 0.05	0.48 ± 0.05	—
Fasting serum insulin (nmol/l)	0.14 ± 0.02	0.15 ± 0.02	—
HOMA insulin resistance index	13.1 ± 1.9	10.7 ± 1.0	—
S-creatinine (μmol/l)	82 ± 2	77 ± 2	—
Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})	108 ± 8	106 ± 4	—
AER (mg/24 h)	4 (1–27)	2 (1–28)	0.058
Current smoking	32	14	0.035
History of smoking	55	27	0.010

Data are means ± SEM or %, except AER, which is given as median (range).

Characteristics of progressors and nonprogressors at follow-up

During the follow-up period, 92% of the progressors ($P = 0.0001$ vs. baseline) and 67% of the nonprogressors ($P < 0.0001$ vs. baseline) had been started on insulin therapy ($P = 0.026$ between the groups at follow-up). Further, progressors could be distinguished from nonprogressors at the follow-up examinations by higher fasting plasma glucose ($P = 0.009$) and HbA_{1c} ($P = 0.006$) concentrations. Otherwise, there were no differences between the variables measured at follow-up. Compared with baseline values, progressors had become more obese ($P = 0.017$), whereas nonprogressors had similar BMIs at baseline and follow-up. Glycemic control had worsened in both groups, as indicated by an increase in HbA_1 concentrations ($P < 0.0001$). Total cholesterol ($P = 0.039$) and HDL cholesterol ($P < 0.0001$) concentrations decreased in nonprogressors but remained unchanged in progressors during follow-up. Fasting C-peptide concentrations increased in both progressors and nonprogressors ($P = 0.009$ and $P < 0.0001$, respectively). The prevalence of macrovascular disease doubled (23 to 52%) during the follow-up period in progressors ($P = 0.011$), and rose from 20 to 32% in nonprogressors ($P = 0.035$) (Table 4).

Predictors of progression of albuminuria

Independent risk factors for progression from normoalbuminuria to micro- or macroalbuminuria were studied with backward step-wise multiple logistic regression analysis. The model included variables that

Table 2—*Baseline prevalence of micro- and macrovascular disease in NIDDM patients with and without progression to micro- or macroalbuminuria during the 9-year follow-up period*

	Progressors	Nonprogressors
n (M/W)	31 (19/12)	59 (23/36)
Retinopathy	19	17
Clinical neuropathy	58	50
Neurophysiological neuropathy	53	16*
Valsalva ratio	1.52 ± 0.07	1.55 ± 0.04
Tilt ratio	1.23 ± 0.04	1.25 ± 0.02
SD of heart rate at rest	39.3 ± 8.6	32.3 ± 2.0
ΔHR at deep breathing	19.8 ± 2.5	20.5 ± 1.4
Macroangiopathy	23	20
Coronary heart disease	19	14
History of myocardial infarction	10	5
History of stroke	0	2
Electrocardiogram hard criteria	6	7
Peripheral vascular disease	6	7
Hypertension	48	46
Antihypertensive treatment	42	37
β-blockers	26	27
Ca-channel blockers	6	4
Diuretics	38	29
Vasodilators	19	12
Other antihypertensive therapy	3	0

Data are % or means ± SEM. ΔHR, difference between maximum and minimum pulse frequency. *P = 0.0004.

were different between progressors and nonprogressors at baseline (male sex, HbA_1, neurophysiological neuropathy, smoking) as well as such well-known risk factors as age, duration of diabetes, systolic blood pressure, baseline AER, retinopathy, and macroangiopathy. Long-term glycemic control (HbA_1) (P = 0.0005) and smoking (P = 0.011) were independent risk factors for progression of albuminuria (Table 5).

CONCLUSIONS

In the present study, 34% of normoalbuminuric NIDDM patients developed micro- or macroalbuminuria during a 9-year follow-up. Glycemic control and smoking predicted the progression of AER.

Could there be a bias in selecting normoalbuminuric NIDDM patients with a diabetes duration of 9 years at baseline? This could be a problem if the most rapid progressors already had micro- or macroalbuminuria at baseline. Niskanen et al. (9) showed that 27% of newly diagnosed Finnish NIDDM patients died during the first 10 years of diabetes. By 10 years' duration, only about 35% of the initial patient cohort remained normoalbuminuric. The finding of the present study should therefore be applied only to the group of patients remaining free of microalbuminuria during the first 10 years. It clearly shows, however, that modifiable risk factors such as glycemic control and smoking, in addition to male sex and neuropathy, influence the progression of albuminuria in those patients with a long microalbuminuria-free interval from diagnosis.

Nineteen percent of the patients died during the follow-up. Selective mortality of progressors during the study could have affected the outcome of the study, as we lack data on AER in most patients who died. The cumulative incidence of progression (34%) was, however, similar to that observed in another Finnish study (36%) with a similar follow-up period (9), which suggests that, if selective mortality exists, this would be a consistent finding in all studies. By extrapolation, this incidence is also similar to the incidence of 23% during a shorter follow-up period of 5–6 years in a Danish study (17). The consistency in cumulative incidence of albuminuria progression between different populations is striking and allows some generalization of the present results.

An important question remains: what does progression of albuminuria reflect in these patients—progression to incipient nephropathy or progression of macrovascular disease? If the latter alternative is true, one would expect both a greater prevalence of macrovascular disease at baseline and a greater incidence of macrovascular disease during the follow-up period among progressors than among nonprogressors. In keeping with some previous studies (16,17), there was no difference in the prevalence of macroangiopathy at baseline between progressors and nonprogressors; neither did baseline macrovascular disease predict progression of AER in the multiple logistic regression analysis.

On the other hand, if the progression of AER indicated development of microangiopathy, one would expect a higher prevalence of other microvascular disease, especially retinopathy, among the progressors at baseline (17,31). In the present study, there was no difference in baseline retinopathy prevalence between the two groups, and neither did retinopathy predict the progression of AER in the logistic regression analysis. Moreover, if progression of AER were a sign of diabetic nephropathy, one would expect a larger number of patients to develop end-stage renal disease during the

Table 3—*Frequency of HLA-DR and immunologic markers in NIDDM patients with and without progression to micro- or macroalbuminuria during the 9-year follow-up period*

	Progressors	Non-progressors
n (M/W)	31 (19/12)	59 (23/36)
HLA types		
HLA-DR1	35	29
HLA-DR2	26	29
HLA-DR3	35	38
HLA-DR4	29	36
HLA-DR3/DR4	61	59
HLA-DR5	19	19
HLA-DR6	6	12
HLA-DR7	23	16
HLA-DR8	10	7
Thyroglobulin antibodies	10	12
Microsomal antibodies	23	23
Parietal cell antibodies	13	5
Islet cell antibodies	16	12

Data are %.

Table 4—*Change from baseline to follow-up examinations 9 years later in progressors and nonprogressors*

	Progressors			Nonprogressors		
	Baseline	Follow-up	*P* value	Baseline	Follow-up	*P* value
n (M/W)	31 (19/12)		—	59 (23/36)		—
Age (years)	58.1 ± 1.1	65.8 ± 1.3	—	57.3 ± 0.8	66.1 ± 0.8	—
Duration of diabetes (years)	10.5 ± 0.8	18.8 ± 0.8	—	8.6 ± 0.6	17.5 ± 0.7	—
Insulin treatment	26	92	0.0001	19	67	<0.0001
BMI (kg/m^2)	26.8 ± 0.7	28.4 ± 0.8	0.017	27.4 ± 0.5	28.0 ± 0.4	—
Systolic blood pressure (mmHg)	152 ± 5	158 ± 4	—	154 ± 3	156 ± 3	—
Diastolic blood pressure (mmHg)	89 ± 2	85 ± 3	—	87 ± 1	87 ± 1	—
Fasting plasma glucose (mmol/l)	12.3 ± 0.6	13.5 ± 1.0	—	9.9 ± 0.4	10.5 ± 0.5	—
HbA_1 (%)	10.8 ± 0.3	12.5 ± 0.4*	<0.0001	9.3 ± 0.2	11.2 ± 0.3*	<0.0001
HbA_{1c} (%)	—	9.4 ± 0.3	—	—	8.4 ± 0.2	—
Triglycerides (mmol/l)	2.47 ± 0.59	2.28 ± 0.40	—	2.24 ± 0.29	1.94 ± 0.14	—
Cholesterol (mmol/l)	6.43 ± 0.37	6.04 ± 0.17	—	6.26 ± 0.18	5.86 ± 0.17	0.039
HDL cholesterol (mmol/l)	1.35 ± 0.09	1.28 ± 0.09	—	1.41 ± 0.05	1.24 ± 0.06	<0.0001
Fasting serum C-peptide (nmo/l)	0.42 ± 0.06	0.63 ± 0.12	0.009	0.48 ± 0.05	0.73 ± 0.06	<0.0001
Fasting serum insulin (nmol/l)	0.14 ± 0.02	0.21 ± 0.08	—	0.15 ± 0.02	0.10 ± 0.01	<0.0001
HOMA-IR index	13.1 ± 1.9	18.2 ± 5.9	—	10.7 ± 1.0	7.3 ± 0.7	—
S-creatinine (µmol/l)	83 ± 2	100 ± 5	0.002	77 ± 2	91 ± 3	0.002
Urinary AER (mg/24 h)	4 (1–27)	—	—	2 (1–28)	—	—
AER (µg/min)	—	43.2 (21.1–2,618)	—	—	6.5 (1.0–20.7)	—
Macroangiopathy	23	52	0.011	20	32	0.035
Hypertension	48	67	0.025	46	53	0.046
Current smoking	32	29	—	14	7	—

Data are means ± SEM or %, except AER, which is given as median (range). *Follow-up HbA_1 values transformed from HbA_{1c} values.

follow-up period. The cumulative incidence of diabetic nephropathy was 10% in the restudied patients compared with the reported prevalence of about 25% after 20 years' duration (32,33). None of the 108 patients in the present study, including those who died during the follow-up period, developed end-stage renal disease. The long duration of diabetes without overt complications could imply that these patients are slow-trackers (34), or protected from diabetic complications. At baseline, there was a higher prevalence of neurophysiologically assessed neuropathy among progressors than among nonprogressors (53 vs. 16%). Although no common pathogenetic mechanism between neuropathy and other microvascular complications has been firmly established, neuropathy generally occurs together with retinopathy and nephropathy, which is most likely explained by the fact that they are strongly associated with glycemic control (35). The worse glycemic control in the progressors may thus further emphasize the observed difference in neuropathy prevalence. Taken together, there is little evidence to support progression of AER mainly as a sign of microvascular disease.

Other possible explanations for the increase in AER could be hyperglycemia per se or insulin resistance. Hyperglycemia has been associated, at least acutely, with an increased AER (36). Poor glycemic control is a consistent risk factor for the early progression of AER in both IDDM and NIDDM patients (9,17,31,37). In support of this finding, glycated hemoglobin was an independent risk factor for the progression of AER in the present study. The beneficial effect of tight glycemic control on the development of microvascular complications has been established in the Diabetes Control and Complications Trial including IDDM patients (38), but it still needs to be confirmed in NIDDM patients (15).

Worsening of insulin sensitivity could provide another explanation for the increase in AER. This is at least partially supported by the tendency toward increased insulin resistance (HOMA index) in the progressors during the follow-up period. Although the HOMA index is a rather crude measurement of insulin sensitivity, it was also associated with worsening of other insulin resistance–linked variables such as BMI and fasting C-peptide levels. In support of this finding, we earlier showed an association between microalbuminuria and insulin resistance in NIDDM and nondiabetic subjects (10,39). In addition,

Table 5—*Variables predictive of progression from normo- to micro- or macroalbuminuria using multiple logistic regression analysis*

Variable	Coefficient	SEM	*P* value
HbA_1	0.716	0.207	0.0005
History of smoking	1.753	0.686	0.011
Male sex	1.337	0.693	0.054
Age	0.119	0.065	0.066
Neuropathy (neurophysiological assessment)	0.929	0.620	0.134

Complete data were available on 90 patients. The model included sex, age, duration of diabetes, history of smoking, systolic blood pressure, HbA_1, ln(AER), macroangiopathy, retinopathy, and neurophysiologically assessed neuropathy.

insulin resistance predicted the development of microalbuminuria in NIDDM patients in a prospective study (40).

Smoking, which is known to be associated with insulin resistance (41), was an independent predictor for the progression of AER in the present study. Smoking has been shown to be associated with worsening of both retinopathy and nephropathy in IDDM patients (42). In NIDDM patients, the results from prospective studies have been conflicting (17,43). This could be due to, e.g., selective mortality of smoking patients.

Similar to our findings, initial blood pressure did not predict the progression of AER in NIDDM patients in a recent Danish study (17). Although most reports have shown an association between blood pressure and albuminuria in cross-sectional studies (8,44) and even an association between prediabetic blood pressure and the risk of subsequent diabetic nephropathy (45), the results from prospective studies have been conflicting (32,46). It is not known whether an increase in blood pressure precedes an increase in AER or vice versa.

Mathiesen et al. (47) have shown that microalbuminuria precedes the increase in blood pressure in IDDM patients. Unfortunately, we cannot provide time-course measurements of blood pressure and AER from diagnosis in our patients.

There was a high prevalence of patients already receiving antihypertensive treatment at baseline, and initiation of antihypertensive therapy during the follow-up period may have altered the progression of AER. However, the prevalence of hypertension was similar in both progressors and nonprogressors at baseline (48 vs. 46%) and at follow-up (67 vs. 53%).

In conclusion, this study reemphasizes the role of glycemic control as a predictor of the progression of AER. Progression of normoalbuminuria to micro- or macroalbuminuria was further associated with male sex, higher basal AER, smoking, and neuropathy.

Acknowledgments — This study was supported by grants from the Finnish Medical Society (Finska Läkaresällskapet), the Finnish Foundation for Diabetes Research of the Finnish Diabetes Association, the Foundation for Life and Health (Liv och Hälsa), the Sigrid Juselius Foundation, and the Perklén Foundation.

We wish to express our gratitude to the late Professor Esko Nikkilä for his valuable advice in planning of the study and to Seija Heikkinen, Marjo Rissanen, Esa Laurila, Marita von Bell, Päivikki Määttälä, and Outi Nikulainen for skilled technical assistance. In addition, we thank Drs. Svante Stenman and Saija Koskimies (HLA-typing), Mauri Lepäntalo and Milla Kallio (assessment of peripheral vascular disease), Paula Summanen and Professor Leila Laatikainen (ophthalmological examination), and Esko Matikainen (neurological examination).

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