The Predictive Value of Microalbuminuria in IDDM

A five-year follow-up study

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OBJECTIVE— To investigate the predictive value of microalbuminuria and the annual increase of albumin excretion as risk factors for diabetic nephropathy.

RESEARCH DESIGN AND METHODS— A 5-year follow-up of patients with microalbuminuria (urinary albumin excretion [UAE] = 30–299 mg/24 h) and matched patients with normoalbuminuria (UAE < 30 mg/24 h). The initial classification was based on one single 24-h urine collection. The annual increase in UAE was calculated by linear regression analysis of log-transformed UAE on time. This study was conducted at the outpatient clinic of the Steno Diabetes Center. The study subjects included 118 insulin-dependent diabetes mellitus (IDDM) patients between 18 and 50 years of age with microalbuminuria and 112 matched control patients with normal UAE with an age at diabetes onset of <31 years. The main outcome measures were UAE, annual change in UAE rate (percentage per year), and the prevalence of retinopathy.

RESULTS— After 5 years, 39 (33%, 24–42 CI [95% confidence interval]) patients with microalbuminuria had normoalbuminuria, 57 (48%, 38–57 CI) still had microalbuminuria, and 22 (19%, 12–27 CI) had developed diabetic nephropathy. Among the 112 patients with normoalbuminuria in 1985, 9 (8%, 4–15 CI) had developed microalbuminuria, and 2 (2%, 0–6 CI) had developed diabetic nephropathy. Of the 79 patients with persistent albuminuria, only 36 (46%, 34–57 CI) were progressors with a rate of progression of >5%/year. Progressors had significantly higher HbA_{1c}, higher mean blood pressure, and a higher incidence of proliferative retinopathy compared with nonprogressors. Multiple regression analysis only identified mean HbA_{1c} as an independent predictor of the rate of progression. Smoking was significantly more prevalent in patients with persistent albuminuria.

CONCLUSIONS— Microalbuminuria is a predictor of progression to diabetic nephropathy; however, not as strong as suggested previously. Calculation of the annual increase in UAE seems to be a more specific method of identifying patients who will develop diabetic nephropathy.

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IDDM, insulin-dependent diabetes mellitus; UAE, urinary albumin excretion; CI, confidence interval; BP, blood pressure; ACE, angiotensin-converting enzyme.

Clinical diabetic nephropathy, characterized by a urinary albumin excretion rate (UAE) > 300 mg/24 h, is the most serious complication of insulin-dependent diabetes mellitus (IDDM) with a large excess of morbidity and mortality (1). A number of studies (2–5) have shown that patients with microalbuminuria, (i.e., UAE = 30–299 mg/24 h) are at high risk for developing diabetic nephropathy.

However, the number of patients studied so far is limited, and most of the studies showing that microalbuminuria is a strong risk marker were conducted before regular measurement of HbA_{1c}, self-monitoring of blood glucose, and aggressive use of antihypertensive treatment were introduced as clinical routine (2–5). Moreover, it is not clear whether the presently defined range of microalbuminuria is optimal (6). Therefore, newer studies on the development of larger groups of patients with microalbuminuria are urgently needed.

In 1985, a cross-sectional study at the Steno Diabetes Center (7), based on the determination of one 24-h urine collection, identified >100 patients with microalbuminuria.

The purpose of this study, in a large group of patients with microalbuminuria and matched control subjects with normoalbuminuria, was to determine the clinical and prognostic implications of microalbuminuria among patients with IDDM controlled by regular visits at a modern outpatient clinic, which aims at strict metabolic control (HbA_{1c} < 7.5%) and starts antihypertensive treatment when blood pressure (BP) is ≥160/95 mmHg.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS— In 1985, 679 consecutive patients with IDDM had one single 24-h urine collection examined for UAE (7). They were ketosis prone with diabetes onset at <31 years of age (between 18 and 50 years of age) and regularly attended the outpatient clinic at the

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Table 1—*Total number, sex, age, age at diabetes onset, and diabetes duration in 1985 in patients with normoalbuminuria and microalbuminuria*

	Patient characteristics			
UAE (mg/24 h)	*n* (M/F)	Age in 1985 (years)	Age at diabetes onset (years)	Diabetes duration in 1985 (years)
<30	112 56/56	35.5 ± 12.7	15.8 ± 6.6	19.6 ± 11.6
30–299	118 58/60	35.4 ± 12.5	14.7 ± 8.0	21.2 ± 13.7

Data are means ± SD.

Steno Diabetes Center. Of the patients, 155 (22.8%) were identified with microalbuminuria, UAE = 30–299 mg/24 h. Among the patients with normol UAE, a matched control group (i.e., matched in pairs with regard to sex, age, and duration of diabetes) was identified. In 1990–1991, 118 of the patients with microalbuminuria and 112 of the patients with normal UAE were still attending the hospital (Table 1). The attendees did not differ from the nonattendees with regard to age, sex, duration of diabetes, number on antihypertensive treatment, or degree of microalbuminuria at entrance in 1985. None of the microalbuminuric patients had progressed to diabetic nephropathy, when last seen in the clinic.

During the 5-year follow-up, the patients were followed according to the hospital routine, which means that they were attending the hospital 3–5 times a year and seeing a diabetes-trained registrar each time. Throughout each year, 1–3 times a year, 24-h UAE was determined. However, three 24-h UAE values each year were available only in ~15% of the patients. HbA_{1c} was determined 2–4 times each year, BP 1 time each year, and direct ophthalmoscopy through the dilatated pupil 1 time each year. Changes in insulin regimen and/or initiation of antihypertensive treatment, as outlined above, were decided by the individual registrar taking care of the patients.

UAE was measured by an enzyme-linked immunosorbent assay technique (8), and HbA_{1c} was measured by high-performance liquid chromatography (9). BP was recorded to the nearest 5 mmHg with a standard sphygmomanometer on the right arm after a 5-min rest. Retinal status was graded according to the following four groups: normal, background retinopathy, proliferative retinopathy, and blind. Patients who developed proliferative retinopathy were laser treated, and, irrespective of the result, they were considered as having proliferative retinopathy in this study. The patients answered questionnaires regarding smoking habits before and during the study period.

Calculations and statistical analysis

The yearly relative change in UAE was calculated as the slope of the linear regression of log-transformed UAE on time. In this calculation, all available UAE values were used, and values were not <8 in any patients. This is given as percentage per year (10). Based on this, the patients were classified as progressors, if they had an increase in UAE of >5%/year and nonprogressors if the increase was less. This cut-off point was applied because normoalbuminuric patients with a rate of progression of >5%/year will develop clinical nephropathy (UAE > 300 mg/24 h) within the following 30 years. If the progression rate is ≤5%, clinical nephropathy will take >30 years to develop. Because, according to epidemiological studies, >95% of IDDM patients who developed clinical nephropathy develop this complication before 30 years of diabetes, we only miss <5% of potential nephropathy if we assume that all potential nephropathy starts to progress UAE at diabetes onset, which probably is not the case. If the progression to nephropathy starts later, the loss of patients will be even less.

Results are given as means ± SD except for UAE, which is given as median with range. Differences between groups were examined with an unpaired Student's *t* test or Mann-Whitney test if the data were not normally distributed. Differences in frequences were examined by the χ^2 test. Results were considered significantly different if $2P < 0.05$.

Within the group of patients having a progression of >5%/year, the dependence of the rate of progression on other variables was studied by multiple

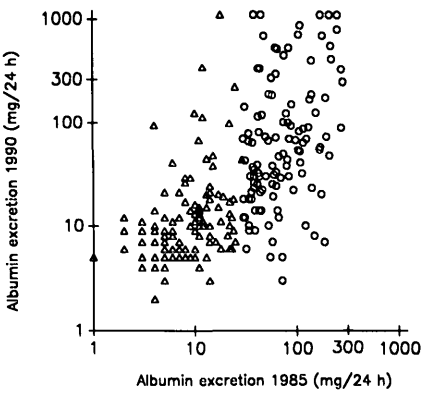

Figure 1—*The relation between individual UAE values of 1985 and 1990 in patients who were normoalbuminuric (△) and microalbuminuric (○) in 1985.*

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Table 2—*Age, diabetes duration, antihypertensive treatment, mean HbA_{1c}, mean BP, and smoking habits in 230 IDDM patients according to UAE after 5 years of follow-up*

UAE (mg/24 h)									Smoking habits *n* (%)		
1985	1990	UAE (mg/24 h) 1985	*n*	Age in 1985 (years)	Diabetes duration in 1985 (years)	Antihypertensive treatment in 1985 *n* (%)	HbA_{1c} (%)	Mean BP (mmHg)	Present	Previous	Never
Ia											
30–299	<30	45* (30–189)	39	33.6 ± 13.8	17.5 ± 14.5	4 (10)	8.4 ± 1.1	92 ± 15	14* (36)	13 (33)	12 (31)
Ib											
<30	<30	8 (1–25)	101	36.1 ± 13.0	20.6 ± 9.2	7 (7)	8.2 ± 0.9	93 ± 10	40* (40)	21 (21)	38 (39)
IIa											
30–299	30–299	78 (30–287)	57	36.1 ± 12.6	19.4 ± 9.7	14 (25)	8.7 ± 0.9	98 ± 9†	36 (63)	8 (14)	13 (23)
IIb											
<30	30–299	14 (4–24)	9	35.9 ± 13.4	18.6 ± 9.9	4 (44)	9.0 ± 0.8†	97 ± 8†	5 (56)	2 (22)	2 (22)
IIIa											
30–299	>299	103.5 (38–276)	22	36.9 ± 10.1	22.8 ± 10.7	13 (56)	9.5 ± 1.7†	101 ± 8†	15 (68)	4 (18)	3 (14)
IIIb											
<30	>299	16 (3–19)	2	36	25	0	9.3†	102†	1	1	0

Data are means ± SD, except UAEs, which are median and (range).
*P <0.01 smaller than IIa and IIIa.
†P < 0.02 higher than Ia and Ib.

linear regression analysis. The following variables were examined as predictors of rate of progression: age, age at diabetes onset, duration of diabetes, log transformed 24-h UAE as of 1985, mean HbA_{1c}, and mean BP.

RESULTS — Of the patients, 118 with microalbuminuria (one single UAE = 30–299 mg/24 h) and 112 with normoalbuminuria (one single UAE < 30 mg/24 h) as of 1985 were followed for 5 years (Table 1).

Among the 118 patients who in 1985 had microalbuminuria, 39 (33%, 24–42 CI [95% confidence interval]) were normoalbuminuric in 1990, 57 (48%, 38–57 CI) remained microalbuminuric, and 22 (19%, 12–27 CI) had developed diabetic nephropathy. Among the 112 patients who in 1985 were normoalbuminuria in 1985, 9 (8%, 4–15 CI) had developed microalbuminuria and 2 (2%, 0–6 CI) developed diabetic nephropathy (Fig. 1). Among the 39 patients who regressed from microalbuminuria to normoalbuminuria, only 14% had >2 UAE values in the microalbuminuric range during the 5-year observation period.

Table 2 presents characteristics of the patients shown in Fig. 1. The median value of UAE in patients with microalbuminuria who regressed to normoalbuminuria was significantly lower than those who remained microalbuminuric or developed diabetic nephropathy (P < 0.02), and the median value of the latter group was significantly higher than those staying microalbuminuric (P < 0.02). However, a very substantial overlap was observed between the three groups.

A much higher proportion of those patients who in 1990 were either microalbuminuric or had developed diabetic nephropathy had been on antihypertensive treatment in the period 1985–1990 (30 and 8%, respectively). Antihypertensive medications used were diuretics, β-blockers, or Ca-channels blockers, but no patients received angiotensin-converting enzyme (ACE) inhibitors. Patients who in 1990 had normal UAE, irrespective of their initial UAE, had similar HbA_{1c} and BP values in the follow-up period. Patients remaining in the microalbuminuric group or developing diabetic nephropathy had significantly higher HbA_{1c} or BP values or both in the follow-up period (Table 2).

The proportion of smokers among patients, who in 1990 were normoalbuminuric irrespective of whether they were normo- or microalbuminuric in 1985, was lower than those staying in the microalbuminuric group or develop-

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Table 3—*Clinical data on patients who from 1985 to 1990 had a rate of increase in UAE >5%/year (progressors) or ≤5%/year (nonprogressors)*

	Progressors	Nonprogressors
n	47	183
Age in 1985 (years)	32.5 ± 12.8	34.4 ± 12.5
Diabetes duration in 1985 (years)	18.5 ± 9.1	19.2 ± 12.0
Mean HbA_{1c} from 1985 to 1990 (%)	9.3 ± 1.3*	8.3 ± 1.0
Mean insulin dosage from 1985 to 1990 (IU/kg)	0.60 ± 0.18	0.59 ± 0.18
Antihypertensive treatment from 1985 to 1990 (*n*)	20 (43%)*	23 (13%)
Mean BP from 1985 to 1990 (mmHg)	98.9 ± 8.8*	93.6 ± 11.1
Proliferative retinopathy or blind in 1985 (*n*)	12 (26%)	32 (18%)
Proliferative retinopathy or blind in 1990 (*n*)	17 (36%)*†	33 (18%)
Smokers in 1990 (*n*)	13 (28%)	59 (32%)

Data are means ± SD.
*$P < 0.01$ progressors higher than nonprogressors.
†$P < 0.01$ those with proliferative retinopathy higher in 1990 than in 1985.

ing diabetic nephropathy. No significant differences with regard to smoking could be detected between those staying microalbuminuric and those developing diabetic nephropathy.

The relative annual rate of increase in UAE (percentage per year) was calculated in all patients, and the patients were divided into progressors, i.e., yearly relative increase in UAE of >5%/year, and nonprogressors, i.e., yearly relative increase in UAE of ≤5%/year. Among the 118 patients with microalbuminuria as of 1985, 36 (31.4%, 22–39 CI) were progressors; however, among the 79 patients with persistent albuminuria, 36 (46%, 35–58 CI) were progressors. Among the 112 patients with normoalbuminuria, 11 (9.8%, 5–17 CI) were progressors. The mean rate of progression did not change with the duration of diabetes; however, in patients with shorter duration of diabetes, a much larger variation in rates of progressions was noted. Because the clinical variables of progressors with normal UAE or microalbuminuria were not statistically different, they are presented as one group. The same applies to the nonprogressors. Table 3 indicates that no difference was found between progressors and nonprogressors with regard to age, duration of diabetes, and insulin dosage. However, the progressors had higher mean HbA_{1c} values in the observation period; only 10% (5 of 47) had mean HbA_{1c} values <8.0%. The progressors also had higher mean BP values, and a higher proportion of these were on antihypertensive treatment. Within the group of progressors, the multiple regression analysis with the six variables as predictors for rate of progression indicated that only mean HbA_{1c} independently contributed to the variation in the rate of progression (R^2 = 0.11). This means that mean HbA_{1c} only explained 11% of the variation in rate of progression.

Among the progressors, the number of patients with advanced retinopathy increased significantly by approximately one third during 5 years, whereas the prevalence of advanced retinopathy was nearly unchanged among nonprogressors. With regard to smoking, no difference was found between progressors and nonprogressors.

CONCLUSIONS— This study shows that during a 5-year follow-up period, 20% of patients with microalbuminuria developed diabetic nephropathy, whereas this applied to only 2% of a matched control group of patients with normal UAE. The study thus confirms that microalbuminuria can be regarded as a risk marker of clinical nephropathy. However, the study also clearly demonstrates the lack of specificity of this risk marker. Only 46% of the patients with persistent microalbuminuria had a progression rate of >5%/year, and only 31% of the patients with persistent microalbuminuria developed diabetic nephropathy during a 5-year observation period. This finding is in contrast with the original observations (2–5) that report that at least 85% of the patients with microalbuminuria developed diabetic nephropathy. In these studies, the identification of patients with microalbuminuria was based on only one urine sample, as in the present study. In the original studies, the observation period was generally longer than 5 years, and this could explain some of the difference, but calculation of the progression rates still suggests that, even given longer observation periods, only 50% will develop diabetic nephropathy. Our finding is, however, in agreement with more recent observations on smaller groups of patients (11–13). Thus, in a prospective study of IDDM patients, only 10 (40%) of 25 patients with persistent microalbuminuria progressed to a higher level of UAE and/or to nephropathy during a 7-year observation period on conventional insulin treatment (11). Also, Jerums (12) demonstrated that some patients with microalbuminuria did not show increasing levels of UAE during many years of follow-up, and in patients with NIDDM and microalbuminuria, progression is seldom seen during 3 years of observation (13). A recent 10-year follow-up study (14) of 20 long-term IDDM patients with microalbuminuria demonstrated progression to overt nephropathy in 28% (10–54 CI). In that study, the duration of diabetes at initial investigation was 26 years, whereas the duration in the earlier studies was 13–19 years (2–5). Therefore, it was suggested that the longer duration of diabetes may be an explanation for the lower figure. In this study, the mean duration of diabetes initially was 16 years, thus differences in duration of diabetes do not explain the

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discrepancies between our study and earlier studies (2–5). Finally, the patients in this study may have been better controlled with regard to mean blood glucose compared with the early studies, and if so, this may be an explanation for the differences. However, this matter cannot be settled because HbA_{1c} values were not available in the early studies.

Of the patients, ~25% were lost to follow-up during the 5 years, and this is a potential weakness in the study. However, approximately the same number of patients were lost in the two groups, and those lost to follow-up did not differ with regard to clinical variables and had not progressed to diabetic nephropathy when last seen in the clinic. We therefore consider it unlikely that, had they been available, those lost to follow-up would have changed the outcome of the study. Among IDDM patients with normal UAE, occasional elevated albumin excretion rates are seen rather frequently. Thus, Mathiesen (15) followed 190 normoalbuminuric nonprogressors and measured UAE 13 times during a 5-year follow-up. Of these patients, 38% experienced at least one UAE in the microalbuminuric range, and 10% sometimes fulfilled the criteria for incipient nephropathy (2 of 3 consecutive samples in the microalbuminuric range) (16). This phenomenon probably also explains why 33% of our microalbuminuric patients were normoalbuminuric at follow-up. Thus, during this study, 1 or 2 UAE values >30 mg/24 h have a low specificity as a risk factor for diabetic nephropathy.

To better identify patients at risk for nephropathy, we therefore prefer a progression rate of albuminuria of 5%/year calculated with at least 5 UAE values obtained during a maximum period of 5 years. Among patients who are persistently microalbuminuric, changes in UAE over time seem to be exponential (10). Therefore, after logaritmic transformation of UAE, trends in changes can be calculated from linear regression analysis. Given an annual rate of increase in UAE of 5%, it would take 30 years to go from normal values (mean 10 mg/24 h) to diabetic nephropathy (>300 mg/24 h). Therefore, anticipating that the rise of UAE starts at diabetes onset, only patients with a rate of progression of >5%/year will reach nephropathy within 30 years, i.e., 10–15 years after the peak incidence of diabetic nephropathy (17). None of our patients developed diabetic nephropathy from one year to the next. The rate of progression based on one or perhaps two yearly measurements of UAE, therefore, seems to be a specific and sufficient way of identifying patients who will progress to diabetic nephropathy.

In this study, the progressors were characterized by poorer glycemic control and a higher BP level compared with nonprogressors during the observation period. Previous studies have suggested that strict glycemic control seems to stop or even revert the progression to diabetic nephropathy (17,18). In the Steno II study (18,19), the difference in mean HbA_{1c} between the two groups was ~1–1.5%. After 5 years of observation, 6 of 18 (35%) patients compared with 1 of 18 (6%) patients with microalbuminuria had progressed to diabetic nephropathy. In this study, the difference in HbA_{1c} between progressors and nonprogressors was ~1%, and this is probably one important explanation for the progression in some patients. Mean BP during the observation period was significantly lower among the nonprogressors compared with progressors. However, in the multiple regression analysis, only HbA_{1c} was an independent predictor of the rate of progression. This is in contrast with a recent study in which antihypertensive treatment was shown to significantly inhibit the progression of incipient nephropathy (20). In this study, ACE inhibitors were used, and it may be, as suggested by the authors, an effect of ACE inhibitors rather than of lowering BP. Whether these differences in HbA_{1c} and mean BP are the only explanation for the fact that some progress and others do not cannot be decided from this study. Other factors, i.e., genetic susceptibility, also may be of importance.

Within the group of progressors, the prevalence of proliferative retinopathy increased significantly during the observation period, whereas retinopathy was rather stable in the group of nonprogressors. This is in accordance with previous observations demonstrating that the incidence of proliferative retinopathy rises sharply just before the onset of diabetic nephropathy (21).

We found a significantly higher proportion of smokers among patients staying microalbuminuric or developing diabetic nephropathy in accordance with other observations (22–24). However, when looking at progressors and nonprogressors, no difference in smoking habits could be seen, which suggests that smoking is only of minor importance for the development of diabetic nephropathy.

In conclusion, this study suggests that an acceptable surveillance with regard to development of microalbuminuria and/or diabetic nephropathy can be achieved with one yearly UAE determination and calculation of the rate of progression. It is suggested that only about half of the patients who become persistently microalbuminuric will develop diabetic nephropathy and that those at risk can be identified by calculating the rate of progression in UAE. Finally, this study supports the importance of metabolic control and BP for the development of diabetic nephropathy.

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