Rapid Progression of Albumin Excretion Is an Independent Predictor of Cardiovascular Mortality in Patients With Type 2 Diabetes and Microalbuminuria

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OBJECTIVE — In patients with type 2 diabetes, microalbuminuria is associated with an increase in predominantly cardiovascular mortality. Considerable interindividual variability in the rate of progression of microalbuminuria exists. The prognostic significance of rate of progression of microalbuminuria with regard to cardiovascular and renal clinical end points is, however, unknown. The purpose of this study was to determine the prognostic significance of rate of progression of microalbuminuria for cardiovascular end points and renal function.

RESEARCH DESIGN AND METHODS — In a previous prospective cohort study, progression of microalbuminuria (expressed as mean yearly change in albumin-to-creatinine ratio) was assessed in 58 patients with type 2 diabetes. During a median follow-up of 7 years after progression of microalbuminuria was determined, we registered all-cause mortality and coronary heart disease mortality as primary end points and coronary heart disease (fatal or nonfatal), peripheral vascular disease, ischemic stroke, retinopathy, macroalbuminuria, and change in serum creatinine as secondary end points.

RESULTS — Seven subjects died during the study; five of these subjects died of coronary heart disease. Cox's regression analysis identified progression of microalbuminuria as a significant predictor of all-cause mortality (hazard ratio 1.46 per point increase in albumin-to-creatinine ratio per year, $P < 0.001$), coronary heart disease mortality (hazard ratio 2.32, $P = 0.006$), and macroalbuminuria (hazard ratio 1.79, $P < 0.001$). Adjustment for multiple cardiovascular risk factors did not affect these results. Identical analyses for baseline level of microalbuminuria instead of progression rate of microalbuminuria did not show significant hazard ratios. In addition, progression of microalbuminuria significantly predicted an increase in serum creatinine ($r = 0.29$, $P = 0.04$).

CONCLUSIONS — In patients with type 2 diabetes and microalbuminuria, the rate of progression of albumin excretion seems to be a powerful independent predictor of mortality caused mainly by coronary heart disease.

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In patients with type 2 diabetes, microalbuminuria is associated with an increase predominantly in cardiovascular mortality (1–5). In this context, microalbuminuria is generally regarded as a risk *indicator* rather than a risk *factor*. Microalbuminuria signals the presence of an atherogenic milieu because of its association with several risk factors for atherosclerosis (6). However, microalbuminuria presumably also represents early generalized vascular (endothelial) damage (7).

Instead of regarding microalbuminuria solely as a binary variable, one can also study dynamic characteristics of microalbuminuria by following its course in time. Considerable interindividual variability exists in the rate of progression of microalbuminuria (8–10). In a previous study, we identified two factors predicting a more rapid rate of progression of microalbuminuria in patients with type 2 diabetes and well-controlled blood pressure: dyslipidemia (high triglyceride, low HDL cholesterol) and the nonuse of angiotensin-converting enzyme inhibitors (11).

The prognostic significance of the rate of progression of albumin excretion within the range of microalbuminuria in type 2 diabetes is unknown. Naturally, rapid progressors will develop macroalbuminuria ("overt nephropathy") earlier than nonprogressors or slow progressors, as has been previously shown in type 1 diabetes (12). However, it is not known whether the rate of progression of microalbuminuria itself has any prognostic significance for cardiovascular or renal clinical end points. Therefore, we followed the subjects participating in our previous study for a median of 7 years.

RESEARCH DESIGN AND METHODS

Determination of rate of progression

All 58 subjects participating in this study were patients with type 2 diabetes who visited the outpatient clinic of our hospital with a good record of attendance. Patients were considered as having type 2 diabetes if they had no history of ketoacidosis, if they were treated by diet alone or

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

in combination with oral hypoglycemic agents, or if they had onset of diabetes after the age of 40 years and a high BMI (>28 kg/m^2). In other cases and in patients beginning insulin treatment at the time of diagnosis of diabetes, a glucagon test was performed and type 2 diabetes was diagnosed if stimulated C-peptide was ≥0.60 pmol/ml. Microalbuminuria was diagnosed based on albumin-to-creatinine ratio of ≥3 and <30 mg/mmol in at least two of three consecutive 24-h urine samples. Microalbuminuria was diagnosed only if this criterion was met in two consecutive triplicate urine samples collected at least 3 months apart. The albumin-to-creatinine ratio was chosen as a parameter of albuminuria, instead of the albumin excretion rate in mg/24 h, to correct for possible sampling errors. Patients were not included if one of the following conditions was present: hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg, with or without antihypertensive treatment), evidence of renal insufficiency (serum creatinine >130 μmol/l), clinically apparent congestive heart failure, or other major illness (e.g., cancer, severe pulmonary disease). The rate of progression of microalbuminuria was monitored in these patients for a period of ≥24 months (mean 34.1 ± 10.2 SD) between January 1989 and August 1996. For the methods used for determination of the rate of progression of microalbuminuria, we refer to our previous study (11). In short, the level of microalbuminuria in these patients was assessed in triplicate 24-h urine samples collected during at least four separate visits. The individual rates of progression of microalbuminuria were calculated by linear regression analysis and expressed as yearly change in albumin-to-creatinine ratio (in mg/mmol per year). All patients had stable metabolic control and controlled blood pressure (<160/95 mmHg) during the period of assessment of microalbuminuria progression.

Table 1—*Baseline characteristics of the 57 patients studied*

Age (years)	58.2 ± 11.0
Sex (% men/% women)	33/24 (57/43)
Duration of diabetes (years)	8.0 (1–28)
BMI (kg/m^2)	29.2 ± 4.4
Systolic blood pressure (mmHg)	143.6 ± 19.0
Diastolic blood pressure (mmHg)	80.8 ± 9.3
Smoking (yes)	16 (28)
Insulin treatment (yes)	34 (59)
Use of angiotensin-converting enzyme inhibitors	26 (46)
Use of other antihypertensives	7 (12)
Coronary heart disease	9 (16)
Retinopathy	26 (50)
HbA_{1c} (%)	8.9 ± 1.5
Serum creatinine (μmol/l)	93.5 ± 19.5
Total cholesterol (mmol/l)	6.0 ± 1.0
Triglyceride (mmol/l)	2.4 (0.7–10.9)
HDL cholesterol (mmol/l)	1.1 ± 0.3
Microalbuminuria (mg/mmol)	8.5 (3.3–27.6)

Continuous data are mean ± SD or, for data with skewed distributions, median (range). Nominal data are presented as *n* (%).

Follow-up

After this first observational period of at least 2 years, during which the progression rate of microalbuminuria was determined, patients were followed for an additional period of at least 4 years, resulting in a total follow-up time from baseline of at least 6 years. The beginning of the period, during which rate of progression of microalbuminuria was assessed in each patient, was considered $t = 0$. As primary end points, we registered mortality and cause of death (coronary heart disease/noncoronary heart disease). As secondary end points, we studied the following: combined fatal and nonfatal coronary heart disease (enzymatically proven myocardial infarction, coronary bypass surgery, or angioplasty), peripheral vascular disease (limb amputation or revascularization procedures), ischemic stroke (confirmed on computed tomography of the brain), retinopathy (proliferative or nonproliferative, diagnosed by yearly funduscopy by an ophthalmologist), macroalbuminuria (median albumin-to-creatinine ratio >30 mg/mmol in at least two of three urine samples), and change in serum creatinine ([serum creatinine concentration at the end of follow-up – serum creatinine concentration at the time of inclusion] ÷ serum creatinine concentration at time of inclusion). During follow-up, urinary albumin-to-creatinine ratio and serum creatinine were measured at least twice yearly.

Analytical methods

Urinary albumin was measured using an immunochemical method on a Behring Nephelometer (Behringwerke, Germany) with interassay coefficient of variation 6.9% at level of 13 mg/l and 4.2% at 75 mg/l and intra-assay variation <2.5% at all levels. Urinary creatinine was measured with a modified Jaffé method. Total cholesterol, triglyceride, and HDL cholesterol levels were measured using enzymatic methods. HbA_{1c} was measured using an automated high-performance liquid chromatography analyzer (Diamat BioRed Laboratories, New York) (normal range 5.2–6.7%).

Statistical analysis

Student's *t* tests of independent samples were used for parametric bivariate analysis of group differences. The independent correlation of change in albumin-to-creatinine ratio with event-free survival was tested by Cox's proportional hazard regression analysis, using the stepwise forward method. The effect of baseline level of microalbuminuria and progression of microalbuminuria on primary and secondary end points was tested independently and adjusted for age and sex as well as for traditional atherosclerotic risk factors, including duration of diabetes, smoking, serum total cholesterol, triglycerides, HDL cholesterol, blood pressure, and HbA_{1c}. The baseline level of the continuous risk factors was taken as the mean of two measurements taken within a period of 3 months at the start of the study. In addition, multiple adjustment was performed using the mean of these risk factor variables during the full period of assessment of progression of microalbumin-

Table 2—*Change in albumin-to-creatinine ratio and baseline values of microalbuminuria in patients who reached any of the predefined end points versus patients who did not*

	End point reached		End point not reached		
	n	Mean ± SD	*n*	Mean ± SD	*P*
All-cause mortality					
Δ*ACR*	7	6.3 ± 5.2	50	1.2 ± 2.8	<0.001
Baseline MA		7.5 ± 3.5		10.3 ± 6.1	0.25
Coronary heart disease mortality					
Δ*ACR*	5	8.9 ± 3.2	52	1.1 ± 2.8	<0.001
Baseline MA		7.1 ± 3.8		10.2 ± 6.1	0.27
Fatal/nonfatal					
Δ*ACR*	13	3.7 ± 5.5	43	1.3 ± 2.6	0.03
Baseline MA		9.3 ± 4.2		9.8 ± 6.0	0.80
Peripheral vascular disease					
Δ*ACR*	6	1.2 ± 3.7	50	1.9 ± 3.6	0.64
Baseline MA		7.1 ± 3.2		10.0 ± 5.8	0.24
Stroke					
Δ*ACR*	4	−1.3 ± 1.6	52	2.1 ± 3.6	0.07
Baseline MA		12.1 ± 1.3		9.5 ± 5.8	0.38
Macroalbuminuria					
Δ*ACR*	14	5.4 ± 3.5	42	0.7 ± 2.7	<0.001
Baseline MA		11.4 ± 6.5		9.1 ± 5.2	0.18

ΔACR = change in albumin-to-creatinine ratio in mg/mmol per year. Baseline MA = baseline value of microalbuminuria in milligram/millimole.

uria. The relation between the change in albumin-to-creatinine ratio and change in serum creatinine was tested by Spearman's rank correlation analysis and by multiple linear regression analysis. Results were considered significant if $P \leq 0.05$.

RESULTS — Of the 58 subjects, 1 patient was lost to follow-up. Baseline characteristics of the 57 patients are shown in Table 1. Seven of the 55 subjects died: 5 due to coronary heart disease, 1 due to metastasized malignancy, and 1 as a result of perforated cholecystitis. Of the patients who remained alive during the study, median follow up was 7 years (range 6–9). The mean change in albumin-to-creatinine ratio (expressed as mg/mmol per year) and the mean baseline values of microalbuminuria of the patients who reached an end point, compared with the patients who did not, are shown in Table 2. Details on secondary end points were not available for one patient who did not visit the outpatient clinic during follow-up but whose survival status could be determined. Mean change in albumin-to-creatinine ratio was significantly higher for both primary end points; for the secondary end points, incidence of fatal/nonfatal coronary heart disease and macroalbuminuria was higher. Mean baseline values of microalbuminuria were not significantly different for any of the primary or secondary end points. Cox's proportional hazard regression analyses were performed to explore the effect of change in albumin-to-creatinine ratio (as a continuous variable) on primary and secondary end points. The results are shown in Table 3. Progression of microalbuminuria was a significant predictor of all-cause mortality, coronary heart disease mortality, and macroalbuminuria. In contrast, change in albumin-to-creatinine ratio did not significantly predict isolated nonfatal coronary heart disease, ischemic stroke, peripheral vascular disease, or incident retinopathy. Multiple adjustment in these analyses for age, sex, duration of diabetes, smoking, baseline levels of serum triglyceride, serum HDL cholesterol, serum total cholesterol, HbA_{1c}, and blood pressure did not significantly change the outcomes. Additional adjustment for baseline level of microalbuminuria and for baseline coronary heart disease yielded virtually identical results (data not shown). In comparison, identical Cox's regression analyses using the baseline level of microalbuminuria as a predictor instead of progression of microalbuminuria showed hazard ratios that were not significant ($P > 0.25$ for all end points). None of the traditional coronary risk factors were predictors of any of the end points to a degree that came close ($P < 0.10$) to statistical significance (data not shown in detail). The same was true when baseline levels of the continuous coronary risk factors were replaced by mean values monitored during the period of assessment of progression of microalbuminuria.

To graphically illustrate the impact of progression of microalbuminuria on sur-

Table 3—*Cox proportional hazard regression analyses of change in albumin-to-creatinine ratio at baseline and after adjustment*

	Univariate			Adjusted*		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Primary end points						
All-cause mortality	1.46	1.18–1.79	<0.001	1.69	1.29–2.21	<0.001
Coronary heart disease mortality	2.32	1.28–4.22	0.006	4.05	1.27–12.9	0.006
Secondary end points						
Fatal/nonfatal coronary heart disease	1.17	1.01–1.36	0.04	1.17	1.01–1.36	0.04
Macroalbuminuria	1.79	1.41–2.28	<0.001	1.79	1.41–2.27	<0.001

Hazard ratios are expressed per 1 mg/mmol per year increase in albumin-to-creatinine ratio. *Adjustment for age, sex, duration of diabetes, smoking, HbA_{1c}, triglycerides, HDL cholesterol, total cholesterol, and blood pressure.

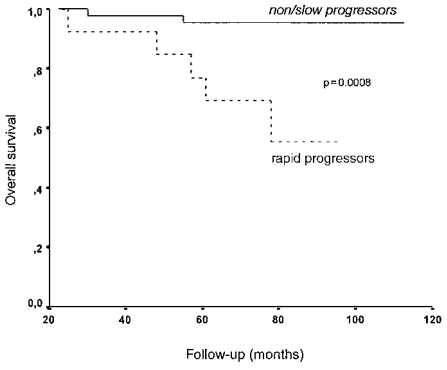

Figure 1—*Kaplan-Meier plot for overall survival in patients with nonprogression or slow progression of microalbuminuria (change in albumin-to-creatinine ratio <4 mg/mmol per year,* top*) and with rapid progression of microalbuminuria (change in albumin-to-creatinine ratio >4 mg/mmol per year,* bottom*; P value by log-rank test).*

vival, Fig. 1 shows the Kaplan-Meier overall survival plot after division of the patients in two categories. The upper line shows patients with nonprogression or slow progression of microalbuminuria (change in albumin-to-creatinine ratio ≤4 mg/mmol per year, $n = 43$), and the bottom line shows patients with rapid progression of microalbuminuria (change in albumin-to-creatinine ratio >4 mg/mmol per year, $n = 14$).

Spearman's rank correlation analysis showed a significant relation between change in albumin-to-creatinine ratio and change in serum creatinine ($r = 0.29$, $P = 0.04$). After adjustment for age, duration of diabetes, systolic blood pressure, diastolic blood pressure, use of angiotensin-converting enzyme inhibitors, smoking, lipids, and BMI by multiple linear regression analysis, change in albumin-to-creatinine ratio remained significantly associated with change in serum creatinine ($P = 0.02$).

CONCLUSIONS — The purpose of our study was to address the prognostic significance of the rate of progression of albuminuria in microalbuminuric patients with type 2 diabetes. Our results suggest that the rate of progression of microalbuminuria is a strong, independent predictor of mortality, especially from coronary heart disease, and decline of renal function. The fact that progression of microalbuminuria predicted cardiovascular morbidity and mortality so clearly, whereas the cohort was too small to demonstrate the effects of traditional atherosclerotic risk factors, suggests that progression of microalbuminuria may be a particularly strong predictor of (short-term) cardiovascular risk.

To our knowledge, this is the first study addressing the prognostic significance of the rate of progression of microalbuminuria in patients with type 2 diabetes with regard to cardiovascular mortality. Forsblom et al. (13) also studied the rate of progression of microalbuminuria in patients with type 2 diabetes. They showed that, during follow-up, the incidence of nonfatal macrovascular disease was higher in progressors than in nonprogressors. Mortality data were, however, not available for their patients.

It is generally acknowledged that microalbuminuria identifies a subgroup of type 2 diabetic patients with a particularly high risk of developing cardiovascular disease. A causal relationship between microalbuminuria and cardiovascular mortality is implausible, and microalbuminuria is generally regarded as a strong risk marker. Our results suggest that the rate of progression of microalbuminuria markedly enhances the prognostic information that one gets from merely establishing the presence or level of microalbuminuria. The study does not provide a pathophysiological explanation for this finding, but it is certainly conceivable that progression of an atherosclerotic risk marker gives more information than does its mere presence or level. Because the presence of microalbuminuria is believed to represent early generalized vascular disease (14), progression of microalbuminuria may well represent progression of early vascular disease, eventually leading to a cardiovascular end point. In other words, our interpretation of the data are that progression of microalbuminuria predicts clinical vascular disease because it reflects progression of preclinical vasculopathy. Although the subgroup of patients with roughly stable microalbuminuria was artificially created, the fact that the 7-year cardiovascular mortality in this group was 0% is intriguing. This finding may even lead to speculation as to whether stable microalbuminuria is a risk marker at all for cardiovascular mortality in patients with type 2 diabetes. Certainly, such speculation requires further studies.

Evidently, patients with rapidly progressive microalbuminuria will convert to overt proteinuria earlier than those with stable microalbuminuria, as is confirmed in our study. However, the level of microalbuminuria has previously been shown to correlate poorly with decline of renal function (15), and glomerular filtration rate may decrease in type 2 diabetic patients who have never had microalbuminuria (16). In addition, recent data cast doubt on the prognostic significance of microalbuminuria for diabetic nephropathy in type 1 diabetes (17). In our study, although it was not a primary end point, we showed a significant relation between progression of microalbuminuria and decline of renal function. We suggest that, as seems true for cardiovascular disease, the association between albuminuria and nephropathy may be stronger when progression rather than presence of albuminuria is studied.

Limitations of our study were the relatively small number of patients and short period of follow-up. However, in a previous study, microalbuminuria seemed to correlate most strongly with short-term (5-year) cardiovascular mortality (18), so this may well be the relevant "period of interest" for a study such as ours. Another limitation could be that mean HbA_{1c} and (systolic) blood pressure in our subjects were, although not unusually high for a hospital-based cohort, certainly not optimal. Therefore, our results may not necessarily be applicable to patients with much better controlled type 2 diabetes. However, subjects of previous studies addressing the impact of (progression of) microalbuminuria on type 2 diabetes had similar levels of glycemic control and blood pressure (4,13,19,20). Another limitation of our study is that, to be included in the study, patients had to remain alive for at least 2 years after the first diagnosis of microalbuminuria to be able to monitor the rate of progression. Although this does not affect our main conclusions, it does introduce a source of patient selection.

In conclusion, compared with simply assessing its presence, monitoring the rate of progression of microalbuminuria may be a better method of identifying patients at risk for cardiovascular disease or decline in renal function.

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