

Significance of Microalbuminuria in Long-Duration Type 1 Diabetes

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OBJECTIVE — The value of microalbuminuria (MA) in predicting renal disease and premature mortality in longer duration type 1 diabetes is unclear.

RESEARCH DESIGN AND METHODS — We followed 135 patients with long-standing type 1 diabetes (>30 years' duration) over a 7-year period, recording albuminuria and other clinical variables. Vital status was ascertained and cause of death was recorded.

RESULTS — A total of 27 of 135 patients (20%) died during the follow-up period. Patients with MA (10 of 30, 33.3%) or proteinuria (5 of 6, 83.3%) at initial examination were more likely to die during follow-up than patients who had normal albumin excretion at baseline (12 of 99, 12%; χ^2 for trend 21.9, $P < 0.0001$). The presence of abnormal albumin excretion and low BMI were independent risk factors of premature death. The causes of death were similar in patients with normal and abnormal urine albumin excretion. A total of 24.4% of initially normoalbuminuric survivors developed MA, and persistent proteinuria developed in 3.5%. Progressors had significantly higher albumin excretion rate at baseline compared with those who remained normoalbuminuric: 9.0 $\mu\text{g}/\text{min}$ (3.8–18) vs. 4.0 $\mu\text{g}/\text{min}$ (0.4–17.5); $P < 0.001$. A total of 21% of patients with MA at baseline reverted to normoalbuminuria, and persistent proteinuria developed in 32%. The likelihood of progression to persistent proteinuria was significantly greater in those with baseline MA compared with those with normal albumin excretion ($P < 0.001$).

CONCLUSIONS — Even in long-standing type 1 diabetes of >30 years' duration, MA and proteinuria predict all-cause mortality. MA is a good predictor of persistent proteinuria.

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The cumulative incidence of diabetic nephropathy, defined as persistent proteinuria, is ~40% after 40 years of type 1 diabetes (1). The incidence increases sharply 10 years after onset of diabetes but is low after 35 years; only 4% develop persistent proteinuria thereafter.

In patients with type 1 diabetes, microalbuminuria (MA) precedes persistent proteinuria and is an accepted early phase of nephropathy (2–4). It is also a risk marker for premature death in these patients, generally from cardiovascular disease (5–8). However, the predictive value

of MA in longer-duration type 1 diabetes has been questioned (9). In a 10-year follow-up of 18 MA patients with duration of type 1 diabetes ≥ 15 years, only 5 patients developed proteinuria and none developed end-stage renal failure. However, in cross-sectional studies, the prevalence of MA in patients with duration of diabetes >30 years is 23–50% (10,14). In one study, these patients with long-duration MA had lower glomerular filtration rates and higher serum creatinine levels than normoalbuminuric patients of similar duration (10). This suggests that even with

long-duration diabetes, patients with MA may be at high risk for progression to end-stage renal failure. There is also insufficient information on the role of MA in predicting premature mortality in patients with MA and long-standing diabetes.

Our aim, therefore, was to determine, in long-standing type 1 diabetes of >30 years' duration, the value of MA in predicting progression of renal disease as well as mortality and morbidity. We also studied the incidence of MA in patients with long-duration diabetes who initially had normal albumin excretion.

RESEARCH DESIGN AND METHODS

Long-standing diabetes was defined as diabetes diagnosed before 41 years of age requiring insulin therapy continuously from within 1 month of diagnosis and with duration of diabetes >30 years. We identified 166 patients meeting these criteria from our diabetes clinic registry in 1994 (10), 140 of whom agreed to provide complete data. There were no other inclusion or exclusion criteria. This study was approved by the Newcastle Health Authority and the University of Newcastle Joint Ethics Committee.

A total of 32 patients (23%) had MA, 6 patients (4%) had overt proteinuria, and 102 patients (73%) were normoalbuminuric at baseline. The Rose questionnaire was used to gather information on the presence of coronary and peripheral vascular disease, and other clinical data were obtained by routine techniques. Proteinuria at baseline was measured by albumin excretion rate (AER) determined in three timed overnight urine samples or three albumin:creatinine ratios (ACRs) estimated in early morning urine samples.

Follow-up

The same group of patients were restudied in 2000. Vital status on 31 December 2000 was ascertained, and for those who died, the cause of death was obtained from death certificates. Data collected at routine clinical annual review for the years 1998–2000 were analyzed. The 3-year averages for BMI, blood pressure, HbA_{1c}, serum creatinine, serum total cho-

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Abbreviations: ACR, albumin:creatinine ratio; AER, albumin excretion rate; MA, microalbuminuria.

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

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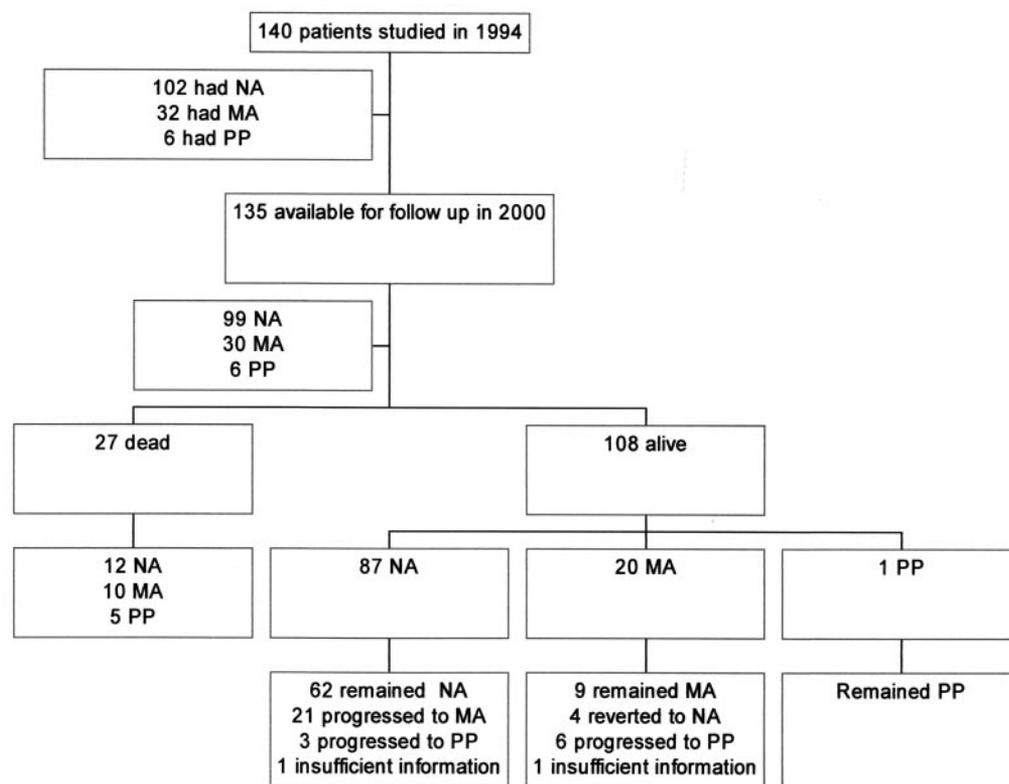


Figure 1—Details of patients studied in 1994 and 2000, including vital status. Patients were stratified into three groups based on their urine albumin excretion at baseline. NA, normoalbuminuria; PP, persistent proteinuria.

lesterol, HDL cholesterol, LDL cholesterol, triglycerides, and urinary ACR (measured on early morning urine samples) were used in the analysis. All patients provided at least two urine samples for analysis during these 3 years. Age, year of diagnosis, current medications, smoking habits, and presence of microvascular and macrovascular disease were recorded. The presence of ischemic heart disease, cerebrovascular disease, or peripheral vascular disease was coded as cardiovascular disease.

Definitions

Normoalbuminuria was defined as AER <20 $\mu\text{g}/\text{min}$ or ACR <2.5 mg/mmol in men and ACR <3.5 mg/mmol in women. MA was defined as two of three AERs 20–200 $\mu\text{g}/\text{min}$ or ACR \geq 2.5 mg/mmol in men and ACR \geq 3.5 mg/mmol in women, with results of urine dipstick test negative for proteinuria. Overt proteinuria was defined as two of three consecutive dipstick test results positive for proteinuria or two of three consecutive AERs >200 $\mu\text{g}/\text{min}$. The term “abnormal albumin excretion” or “albuminuria” was used to describe patients with MA or overt proteinuria. A change in albuminuria status on follow-up was based on presence of at least two of three values in the relevant range.

Laboratory analysis

Urine albumin excretion was determined by sensitive single antibody radioimmunoassay method. HbA_{1c} was measured by enzyme immunoassay (reference range 4.4–5.2%) at baseline and by ion exchange liquid chromatography (reference range <6.1%) at follow-up. The follow-up HbA_{1c} results are NSPG-certified. Other analytes were measured by standard automated techniques.

Statistical analysis

SPSS/PC statistical software (SPSS, Chicago, IL) was used for analysis. Serum triglyceride concentrations, AER, and ACR were normalized by logarithmic transformation before analysis. Values are given as means \pm SD or median (range). Differences between groups were assessed using Student's *t* test or χ^2 test as appropriate. Differences in survival were assessed using Kaplan-Meier analysis, and factors related to death were analyzed by Cox multiple regression analysis with months of survival as the dependent variable.

The baseline factors contributing to progression of albuminuria and development of cardiovascular disease were analyzed by binary logistic regression analysis using follow-up ACR and cardiovascular disease status as dependent variables, re-

spectively. A two-tailed *P* value <0.05 was considered significant.

RESULTS

Abnormal albumin excretion and vital status

Information about vital status was available on 135 of the initial 140 patients (96.4%): 99 had normoalbuminuria at baseline, 30 had MA, and 6 had proteinuria. No follow-up information was available on three initially normoalbuminuric patients and two patients with MA. A total of 27 of 135 patients (20%) died during follow-up (Fig. 1). Patients with MA (10 of 30, 33.3%) or proteinuria (5 of 6, 83.3%) at initial examination were more likely to die during follow-up than patients who had normal albumin excretion at baseline (12 of 99, 12%; χ^2 for trend 21.9; *P* <0.001). The proportion of deaths in the MA group was also higher than in the normoalbuminuric patients (χ^2 5.9, *P* = 0.01) (Fig. 2).

In univariate analysis, the patients who died during follow-up had higher serum creatinine levels and higher percentage of abnormal albumin excretion and cardiovascular disease at baseline (Table 1). There was no significant difference in any other baseline variable.

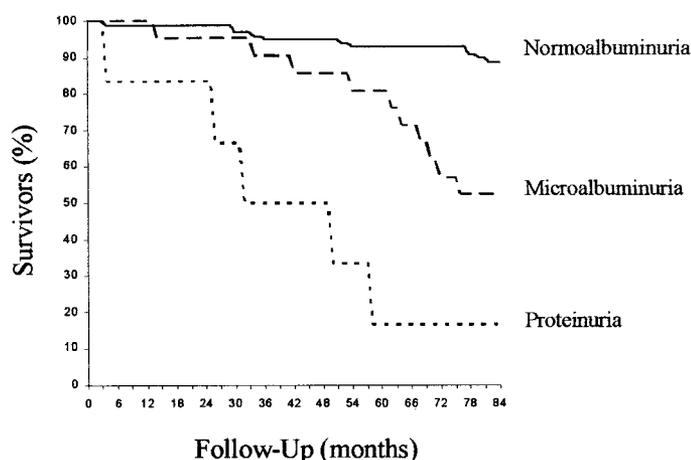


Figure 2—Kaplan-Meier cumulative survival analysis in 135 patients with long-duration type 1 diabetes followed from January 1994 to December 2000 (84 months). Patients were categorized by baseline albumin excretion (group 1, normoalbuminuric patients; group 2, MA patients; group 3, persistent proteinuric patients). χ^2 for trend 21.9; $P < 0.001$. Normoalbuminuria versus MA: χ^2 5.9; $P = 0.01$.

Cox multiple regression analysis was performed with months of survival as the dependent variable and the baseline factors described in Table 1 as predictors entered into the model. Only the presence of abnormal albumin excretion and lower BMI were independent risk factors for premature death (Table 2).

There were 13 (48%) deaths from cardiovascular causes, 7 (26%) due to infection, and 3 (11%) due to malignancies. The cause of death could not be ascertained in one patient. The cause of death

did not differ in the different albuminuric groups (χ^2 for trend 4.9, $P = 0.3$). Three patients who died of infection were on renal replacement therapy before their terminal illness. One other patient who underwent successful renal transplantation died of cardiovascular disease.

Change in albuminuria status in survivors

Sufficient follow-up information was available on 106 of 108 survivors. A total of 86 survivors were normoalbuminuric

at baseline, 62 of whom (72%) remained normoalbuminuric at follow-up. A total of 21 patients (24.4%) had progressed to MA, and 3 patients (3.5%) had progressed to persistent proteinuria. Therefore, the cumulative incidence of developing abnormal albumin excretion was 27.9% in 7 years. Those who subsequently developed MA or proteinuria had significantly higher baseline AER compared with those who remained normoalbuminuric [median 9.0 $\mu\text{g}/\text{min}$ (3.8–18.0) vs. 4.0 $\mu\text{g}/\text{min}$ (0.4–17.5); $P < 0.001$]. Baseline serum triglyceride levels were significantly higher in those who developed albuminuria ($P = 0.01$), as were serum creatinine levels at follow-up (92 ± 13 vs. 100 ± 16 , $P = 0.047$). Other clinical parameters were similar at baseline and follow-up in progressors and nonprogressors (Table 3). Baseline AER [odds ratio 1.8 (95% CI 1.19–2.73), $P = 0.006$] was the only independent predictor of progression by binary logistic regression analysis performed with all baseline variables entered into the model.

In the group with MA at baseline, four patients (21%) had normal albumin excretion at follow-up, nine patients (47%) remained microalbuminuric, and six patients (32%) developed persistent proteinuria. The one surviving patient with proteinuria at baseline still had proteinuria at follow-up. The likelihood of progression to persistent proteinuria was significantly greater in those with baseline MA compared with those with normal albumin excretion (χ^2 10.9, $P < 0.001$). The number of patients with MA was too small for further analysis.

Table 1—Baseline data on long-duration type 1 diabetic patients who died or survived during a 7-year follow-up

	Dead	Alive	P
n	27	108	
Age (years)	59.6 \pm 12.8	56.4 \pm 10.5	0.23
Men:women	17:10	71:37	0.78
Duration of diabetes (years)	39.1 \pm 6.8	37.7 \pm 6.8	0.35
BMI (kg/m^2)	25.4 \pm 3.5	26.2 \pm 3.4	0.32
Systolic blood pressure (mmHg)	148 \pm 22	143 \pm 21	0.25
Diastolic blood pressure (mmHg)	77 \pm 12	77 \pm 9	0.99
HbA _{1c} (%)	7.2 \pm 2	6.9 \pm 1.3	0.4
Serum creatinine ($\mu\text{mol}/\text{l}$)	124 \pm 78	91 \pm 27	0.041
Total cholesterol (mmol/l)	5.7 \pm 1.2	5.5 \pm 1.1	0.36
Triglycerides (mmol/l)	1.5 (0.4–4.3)	1.1 (0.3–8.2)	0.07
Abnormal albumin excretion (%)	59	18.5	<0.001
Smoking (%)	56	43	0.22
Preexisting cardiovascular disease (%)	67	39	0.009
Use of antihypertensive medication	12 (44)	28 (26)	0.06
Use of ACE inhibitors	6 (22)	16 (15)	0.35

Data are means \pm SD, median (range), or n (%). Student's *t* test or χ^2 test used as appropriate. Serum triglycerides analyzed by Mann-Whitney *U* test.

Abnormal albumin excretion and cardiovascular disease

In survivors, 35% (31 of 86) of the normoalbuminuric group had cardiovascular disease at baseline compared with 53% (10 of 19) in the MA group (χ^2 2.0, $P = 0.15$). At follow-up, the proportions were 44% (38 of 86) and 74% (14 of 19), respectively (χ^2 5.4, $P = 0.02$). The one surviving patient with proteinuria at baseline also had cardiovascular disease. Therefore, the overall cardiovascular prevalence in survivors was 50% (53 of 106) by follow-up.

In univariate analysis, baseline serum creatinine (85 ± 21 vs. 95 ± 24 $\mu\text{mol}/\text{l}$, $P = 0.03$), BMI (25.1 ± 3.1 vs. 27.3 ± 3.5 kg/m^2 , $P = 0.001$), and serum triglycerides (median 1.1 vs. 1.6 mmol/l , $P =$

Table 2—Baseline factors independently associated with premature death in long-duration type 1 diabetic patients using Cox multiple regression analysis

Baseline variable	Odds ratio	95% CI	P
Albuminuria	3.8	1.89–7.64	<0.001
BMI	0.86	0.75–0.99	0.03
Preexisting cardiovascular disease	2.00	0.79–5.08	0.15

0.02) were significantly higher in survivors who developed cardiovascular disease by follow-up. Binary logistic regression analysis was performed, using cardiovascular disease at follow-up as the dependent variable and with baseline age, duration of diabetes, BMI, blood pressure, HbA_{1c}, serum creatinine, serum total cholesterol, serum triglycerides, presence of abnormal albumin excretion, preexisting cardiovascular disease, and smoking entered into the model. There were no independent risk factors identified for development of cardiovascular disease.

CONCLUSIONS— Our results suggest that MA remains a strong predictor of all-cause mortality in patients with long-duration type 1 diabetes, independent of other recognized risk factors. The relative risk of premature death in microalbuminuric compared with normoalbuminuric long-duration patients is at least as great as in type 1 diabetic patients with shorter

duration of disease (5–8) and type 2 diabetic patients (11,12). The reason for the association of MA with premature death is not clearly understood, although family studies have shown an increased prevalence of cardiovascular disease, dyslipidemia, and hypertension in first-degree relatives of type 1 diabetic patients with MA (13), suggesting a genetic influence.

It is evident from our data that the presence of albuminuria and low BMI are independent risk factors for premature death. Parving et al. (27) found that abnormally increased albumin excretion, hypertension, smoking, and poor glycaemic control predicted mortality in their series of type 1 diabetic patients of shorter duration. There were no data on BMI or preexisting cardiovascular disease in that study. Our observation that low BMI correlates with premature death could be due to cachexia, which preceded death in these patients.

Orchard et al. (14) reported the cross-

sectional prevalence of ischemic heart disease to be low (10%) after 30 years of type 1 diabetes, with a much higher prevalence of peripheral vascular disease, especially in women (~30%). The 50% prevalence of cardiovascular disease in our series could be due to the longer duration of diabetes and higher mean age. It should also be noted that we included ischemic heart disease, cerebrovascular disease, and peripheral vascular disease in the definition of cardiovascular disease.

It is well known that patients with overt proteinuria are at extremely high risk for macrovascular disease (15–17). In addition, even patients with MA have been shown to have 2.5 times higher risk of atherosclerotic vascular disease than those with lower excretion rates, independent of other atherogenic risk factors (5). However, a similar association between MA and increased risk of cardiovascular disease was not observed in the survivors in our series nor was there an excess of deaths from cardiovascular causes, although numbers were small. In addition, the prevalence of cardiovascular disease may have been underestimated at baseline because of the use of the Rose questionnaire.

Our results demonstrate that MA is a good predictor of proteinuria, even in patients with long-duration type 1 diabetes.

Table 3—Baseline and follow-up characteristics in initially normoalbuminuric long-duration type 1 diabetic patients who did (progressors) or did not develop abnormal albumin excretion (nonprogressors) during 7-year follow-up

	Baseline		Follow-up	
	Nonprogressors (62)	Progressors (24)	Nonprogressors	Progressors
Age (years)	55 ± 10	60 ± 11		
Men:women	38:24	18:6		
Duration of diabetes (years)	37 ± 7	39 ± 6		
BMI (kg/m ²)	25.7 ± 3.5	25.7 ± 2.5	26.4 ± 3.8	26.7 ± 3.6
Systolic blood pressure (mmHg)	141 ± 20	142 ± 21	145 ± 17	145 ± 20
Diastolic blood pressure (mmHg)	75 ± 8	78 ± 9	75 ± 9	75 ± 8
HbA _{1c} (%)	6.8 ± 1.0	7.0 ± 1.7	8.5 ± 1.0	8.5 ± 1
Serum creatinine (μmol/l)	85 ± 22	92 ± 24	92 ± 13	100 ± 16*
Total cholesterol (mmol/l)	5.4 ± 1.0	5.8 ± 1.5	5.5 ± 0.9	5.7 ± 1.1
Triglycerides (mmol/l)	1.0 (0.3–3.1)	1.4 (0.6–3.5)†	1.2 (0.5–3.2)	1.6 (0.6–4.1)
AER at baseline (μg/min)	4.0 (0.4–17.5)	9.0 (3.8–18.0)‡		
ACR at follow-up (mg/mmol)			0.55 ± 0.76	14.54 ± 35
History of smoking (%)	37	46		
Preexisting cardiovascular disease	36	38	42	50
Treatment for hypertension (%)	19	37	45	61
Lipid-lowering agents (%)	3	8	19	39

Data are means ± SD or median (range). *P = 0.047; †P = 0.027; ‡P < 0.001. For HbA_{1c}, note that the assays used were enzyme immunoassay (reference range 4.4–5.2%) at baseline and ion exchange liquid chromatography (reference range <6.1%) at follow-up. Student's *t* test or χ^2 test were used as appropriate. Serum triglycerides and AER were analyzed by Mann-Whitney *U* test.

This is in apparent contrast to a previous report in which a small number of type 1 diabetic patients with duration of diabetes >15 years were followed for 10 years (9). However, in that series, the cumulative incidence of proteinuria was 27.8% in 10 years, i.e., 2.8% per annum, compared with 27.9% in 7 years (4% per annum) in this current study. The patients in the present study were much older and had longer duration of disease than the Forsblom study. Although earlier studies suggested that ~80% of type 1 diabetic patients with MA would develop proteinuria (2–4), more recent studies suggest that in ~30% of MA patients, albumin excretion reverts to normal, 50% remain microalbuminuric, and 20% progress to proteinuria over a 5- to 9-year period (18–20). Our results suggest that MA patients with long-duration diabetes follow a similar pattern and are at least as likely to progress as patients with shorter duration of disease.

Older epidemiological data suggest that the incidence of proteinuria in type 1 diabetes has two peaks: one after 16 years and the other after 32 years, with patients surviving >35 years having a low risk (1). However, a larger follow-up study showed a decreasing incidence in persistent proteinuria, with peak incidence after 15–17 years of diabetes duration and most patients remaining free of proteinuria after 40 years of disease. Our data suggest that this may no longer be true, for two reasons. First, as described above, a significant proportion of type 1 diabetic patients with MA and diabetes duration >30 years progressed from MA to proteinuria during follow-up. Second, 27.9% of our initially normoalbuminuric patients developed MA during follow-up, i.e., annual incidence of 4.0%. This is much higher than the annual incidence of 1.5–2.5% reported in populations of mixed diabetes duration (21–23,29) and the cumulative incidence of 5.8% over 4 years described in type 1 diabetes of >20 years' duration (33). Therefore, it appears that patients with long-duration type 1 diabetes still remain at risk for progression to MA and proteinuria.

One reason for this apparent discrepancy between historical and newer data is that the natural history of diabetic nephropathy is changing. The cumulative prevalence of MA has apparently decreased from 45–50% after 15–29 years' duration of diabetes in cohorts studied in

1985–1986 (26,27) to 30–40% in cohorts studied later (24,31). Similarly, the cumulative incidence of proteinuria is also apparently decreasing, from 40–50% after 15–29 years' duration in cohorts diagnosed from 1933–1972 (30) or 1939–1959 (25) to 17–20% in later cohorts (24,27). Although at first sight this could mean that diabetic nephropathy is being prevented, the data presented in this paper suggest that this is not the case and that the onset of diabetic nephropathy is being delayed rather than prevented. Therefore, new cases may continue to appear in long-duration patients more frequently than previously believed. Reasons for delayed onset might reflect general improvements in diabetes care, particularly in glycemic and blood pressure control. It is noteworthy that in a recent meta-analysis, the beneficial effects of ACE inhibition on MA seem to wane after 4 years (28). In addition, tight glycaemic control in the Diabetes Control and Complications Trial (DCCT) did not completely prevent the appearance of MA (18).

Interestingly, the baseline AER was significantly higher in patients who progressed to MA compared with patients who remained normoalbuminuric. Our results are in agreement with previously documented findings in other populations that elevated baseline urinary excretion rates, even within the normoalbuminuric range, have a clear effect on progression (18,19,29).

Our results show that even in long-standing type 1 diabetes of >30 years' duration, MA and proteinuria predict all-cause mortality. Contrary to previous studies, MA was found to be a good predictor of future progression to proteinuria.

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