

Systolic blood pressure relates to the rate of progression of albuminuria in NIDDM

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Summary We prospectively followed a cohort of 278 non-insulin-dependent (NIDDM) patients for a 6-year period, intending to estimate the rate of increase of albuminuria and to identify clinical variables that influence this increase. At baseline, normoalbuminuria (N) was seen in 74 %, microalbuminuria (M) in 19 % and 7 % presented with proteinuria (P). A total of 80 patients died; they were older ($p < 0.001$) and had higher albumin excretion both at baseline and as an average during follow-up ($p < 0.01$). At baseline, patients with proteinuria had higher blood pressures (systolic and diastolic), whereas there was no difference between patients with normo- and microalbuminuria. Glycaemic control was increasingly poor throughout the three groups. At follow-up, an average relative rate of increase of albuminuria (slope) of 17 % per year was seen both for patients with complete 6 years, follow-up ($n = 135$) and patients with at least 4 years follow-up ($n = 178$). Slope correlated significantly with systolic blood pressure ($r = 0.26$ and 0.29) in both groups, diastolic blood pressure only in the 4-year group

($r = 0.22$) and average albuminuria in both ($r = 0.31$ and 0.24). By multiple regression analyses systolic blood pressure and average albuminuria remained with significant influence on slope. Progression was defined as an increase in the category (e.g. normo- to microalbuminuria) as well as an increase of more than 20 % in albumin excretion, and was seen in 46 patients with at least 4 years' follow-up. Progressors (patients demonstrating progression) had higher systolic blood pressure ($165 \text{ mm Hg} \pm 20$ vs 156 ± 17) and poorer glycaemic control ($\text{HbA}_{1\text{C}}$: $8.2 \% \pm 1.5$ vs 7.7 ± 1.3) $p < 0.05$, as well as a higher level of albuminuria at baseline. The present study points to systolic blood pressure and general level of albuminuria as factors determining the rate of progression of albuminuria. However, only a modest fraction of the variation between subjects was explained by these variables. [Diabetologia (1994) 37: 1251–1258]

Key words Non-insulin-dependent diabetes mellitus, albuminuria, blood pressure, rate of progression, progressors, glycaemic control.

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Abbreviations: IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; N, normal urinary albumin excretion; M, microalbuminuria; P, proteinuria; Slope, relative rate of increase; UAC, urinary albumin concentration; UAE, urinary albumin excretion rate.

The natural development of diabetic nephropathy pertaining to patients with non-insulin-dependent diabetes (NIDDM) is poorly elucidated [1, 2]. In insulin-dependent diabetes (IDDM) approximately 30 % of patients eventually develop end-stage renal failure [3], whereas in NIDDM the proportion is much lower (less than 10 %) at least in elderly Caucasian populations [4–7]. Persistent microalbuminuria (i.e. a urinary albumin excretion (UAE) from $20 \mu\text{g}/\text{min}$ to $200 \mu\text{g}/\text{min}$) in patients with IDDM defines the state of incipient nephropathy [3], which is the state from which approximately 80 % progress to overt nephropathy over the next decade. Microalbuminuria

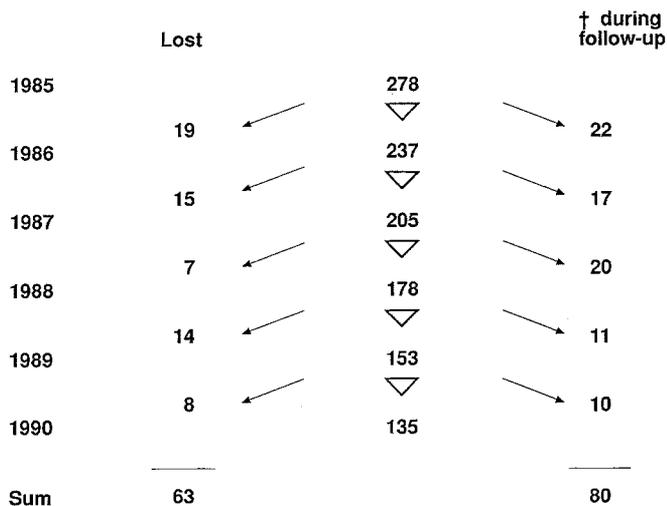


Fig. 1. Fate of the initial cohort during the 6-year observation period. Twenty-four per cent of those with normal urinary albumin excretion, 35 % of normoalbuminuric and 60 % of patients with proteinuria died

and proteinuria in NIDDM are frequent (20–40 % and 5–15 %, respectively) [4, 6–11], and often present at diagnosis or at early known durations [4, 11–16]. Microalbuminuria in NIDDM obviously do also predict the development of clinical proteinuria [17], which will progress in some cases to renal failure, but with far less consistency than is seen in IDDM [18]. The state of incipient nephropathy has hence not been specified in NIDDM. The main enigma is that microalbuminuria in NIDDM is not as closely linked with microvascular complications [19] as it is in IDDM. The predominant implication of microalbuminuria in NIDDM is the strong independent prediction of increased mortality, which is due mainly to cardiovascular causes [6–7, 20–21].

The evolution of urinary albumin excretion in NIDDM has previously been sparsely studied, and we found it of interest to prospectively follow-up a cohort of elderly outpatients with this type of diabetes. Our aim was to estimate the rate of progression of albuminuria and the influence of potential clinical risk factors.

Subjects and methods

All Caucasian diabetic patients attending our outpatient clinic during 1985, who were born during the period 1914–1934 were followed until the end of 1990. A total of 401 such patients were seen, 278 of whom were considered non-insulin-dependent by the following criteria: age at diagnosis 40 years or over, and treated without insulin for a period of more than 2 years.

Urinary albumin concentration (UAC) was measured by radioimmunoassay [22] in early morning urine samples at each attendance during the study period. The average UAC was calculated for each year. Mean number of measurements per person per year was 3.3 (2.9–3.7, range for years). Fasting plasma glucose was measured by standard enzymatic tech-

Table 1. Overview of subjects by number of years of follow-up and level of urinary albumin excretion at baseline

Years	Urinary albumin concentration ($\mu\text{g/ml}$)			
	≤ 15	$> 15 - \leq 200$	> 200	
6	108	24	3	135
5	11	5	2	18
4	17	5	3	25
3	21	5	1	27
2	21	5	6	32
1	28	8	5	41
	206	52	20	278

nique, and the level of glycaemic control was described as mean during year of entrance, mean through the study period and mean of all values obtained since the diagnosis of diabetes. Haemoglobin A_{1c} (HbA_{1c}) was measured by HPLC [23], and blood pressure after 5 min sitting was measured by a conventional sphygmomanometer with phase V for diastolic value. Mean values of these parameters were obtained through the study period. Antidiabetic and antihypertensive or diuretic therapy were currently recorded. Treatment modality was designated as the most “intensive” during the study period; insulin > oral hypoglycaemic agents diet.

Figure 1 delineates the fate of the initial cohort, indicating the number of patients who died or left the study. Table 1 describes the patients by number of years of follow-up and category of albuminuria at baseline (average during 1985). Normoalbuminuria defined as UAC $\leq 15 \mu\text{g/ml}$ was seen in 74 %; microalbuminuria ($15 \mu\text{g/ml} < \text{UAC} \leq 200 \mu\text{g/ml}$) was seen in 19 %; and 7 % presented with proteinuria (UAC $> 200 \mu\text{g/ml}$).

The patients gave their informed consent and the study was performed in accordance with the Declaration of Helsinki.

Statistical analysis

For each individual the rate of progression of albuminuria was estimated from a linear regression of the annual average UAC on year of follow-up. Here and elsewhere UAC measurements were \log_{10} transformed prior to any calculations and is therefore given as geometric mean \times / \pm tolerance factor. Simple (unweighted) linear regression was used, as preliminary calculations indicated that these results were essentially identical to results from a weighted linear regression using number of measurements each year as weights. The regression coefficient estimates the *relative rate of increase of UAC*, when calculated as $(\exp\{\text{regression coefficient} \times \ln(10)\} - 1) \times 100\%$. This measure of progression of albuminuria is simply called “slope”. Patients with few years of follow-up present with uncertain estimates of slope, due to a considerable intra-individual variation of UAC. At the same time patients with complete follow-up constitute a highly-selected group. To better elucidate the relative importance of these issues, all calculations were performed on three categories of subjects: those with at least 2 years of follow-up, those with at least 4 years of follow-up, and those with a complete 6-year follow-up, respectively.

The purpose of the analysis was to identify factors which could explain the interindividual variation in the slope estimates. Initially each clinical variable was assessed separately using *t*-test or one-way analysis of variance for categorical variables and correlation coefficients for quantitative variables. A multiple regression with slope as the dependent variable was finally performed in order to identify independent prognostic factors. To evaluate whether the relative rate of in-

Table 2. Clinical data. Number or mean (range)

	Normo-albuminuria	Micro-albuminuria	Proteinuria
Sex (male/female)	107/99	32/20	11/9
Age (years)	63.8 (51–71)	64.7 (54–71)	63.9 (51–71)
Known diabetes duration (years)	7.4 (0–26)	9.5 ^b (0–28)	8.7 (1–23)
Body mass index (kg/m ²)	28.2 (17.6–48.3)	28.5 (16.8–55.9)	31.5 ^c (18.8–45.5)
Plasma glucose (mmol/l) B	9.1 (4.9–18.2)	9.6 (5.1–13.5)	10.3 (6.5–21.4)
Plasma glucose (mmol/l) S	9.4 (5.6–18.4)	9.7 (5.2–15.1)	10.6 ^b (6.4–16.8)
Plasma glucose (mmol/l) A	8.8 (5.6–17.7)	9.4 ^b (5.7–17.4)	10.0 ^c (5.8–14.1)
HbA _{1c} (%)	7.7 (5.3–13.1)	8.4 ^c (5.4–11.8)	8.2 (7.2–9.9)
Blood pressure			
systolic (mm Hg)	155 (110–213)	158 (110–207)	171 ^{a,c} (141–210)
diastolic (mm Hg)	87 (65–120)	87 (60–104)	92 ^{a,b} (70–111)
UAC (µg/ml)	4.5 (0.4–15)	38.7 (16–149)	560.5 (204–1603)
Treatment (D/T/I)	35/145/26	5/33/14	2/13/5
AH (%)	43	62	70

^a $p < 0.05$ vs M; ^b $p < 0.05$ vs N; ^c $p < 0.01$ vs N.

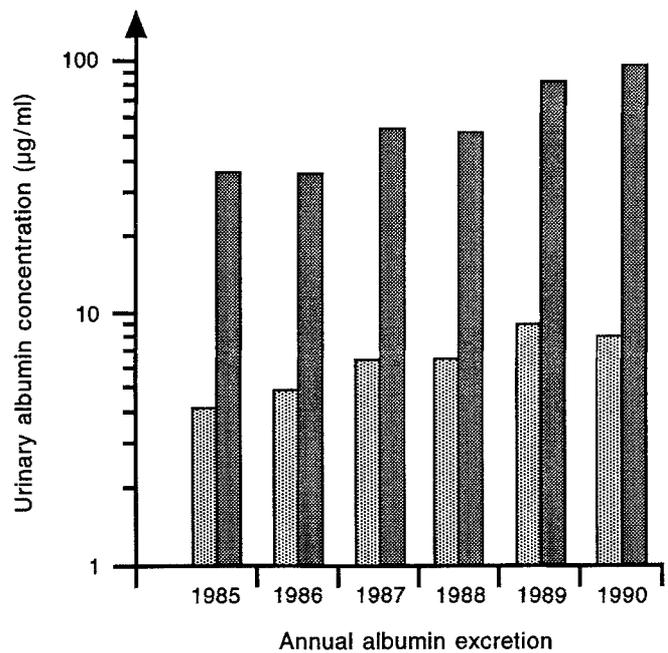
B/S/A, Baseline/study period/all; D/T/I, Diet/Tablet/Insulin; AH, Antihypertensive/diuretic treatment

Table 3. Correlations between clinical variables and albuminuria at baseline including all subjects. Significant associations ($p < 0.05$) are indicated by bold figures

		Baseline albuminuria
Age	(B)	0.070
Diabetes duration	(B)	0.108
Body mass index	(S)	0.183
Plasma glucose	(B)	0.131
	(S)	0.134
	(A)	0.197
HbA _{1c}	(S)	0.172
Blood pressure		
systolic	(S)	0.168
diastolic	(S)	0.151

crease was associated with the level of albuminuria, the average UAC during follow-up was computed for each individual and used as an independent variable in the analyses. Unlike baseline UAC the average will not give rise to a "regression towards the mean" phenomenon.

It is well known that among diabetic patients some develop vascular complications, whereas others do not. The present group of patients may therefore be viewed as a mixture of two "subpopulations", and we performed additional analyses from this perspective. "Progressors" were defined as those patients who exhibited an increase in the category of albumin excretion (e.g. normo- → microalbuminuria) as well as an increase of more than 20% from baseline. The two groups, progressors

**Fig. 2.** Average annual albumin excretion in 108 patients with normal urinary albumin excretion (hatched bars) and 24 with micro-albuminuria (solid black bars) at baseline, who completed the 6-year follow-up

and non-progressors, were then compared with respect to the distribution of the clinical variables.

Results

Clinical characteristics of the patients appear in Table 2. Patients with proteinuria exhibited both higher systolic as well as diastolic blood pressure, but blood pressure was similar in patients with normal urinary albumin excretion and microalbuminuria. Glycaemic control was increasingly poor throughout the three groups, as evaluated by plasma glucose values. HbA_{1c} was similarly elevated in micro-albuminuric and proteinuric patients. Insulin was required in 13%, 27% and 25%, respectively. Correlations between clinical parameters and urinary albumin excretion at baseline including all subjects appear in Table 3, and associations with albuminuria at baseline and average for patients with complete 6-years follow-up are presented in Table 4. Average albuminuria was significantly associated with glycaemic control and systolic blood pressure.

The average annual albumin excretion for patients who completed the 6-year follow-up are shown in Figure 2. Those with normal UAC rose from 4.2 µg/ml $\times / \div 1.9$ to 8.3 $\times / \div 2.8$, $p < 0.0001$, and micro-albuminuria increased from 36.4 µg/ml $\times / \div 1.9$ to 96.9 $\times / \div 4.0$, $p < 0.01$. The individual courses of the microalbuminuric patients are given in Figure 3, which also demonstrates the intraindividual variation. The relative rate of increase in urinary albumin excretion was estimated for patients with values for

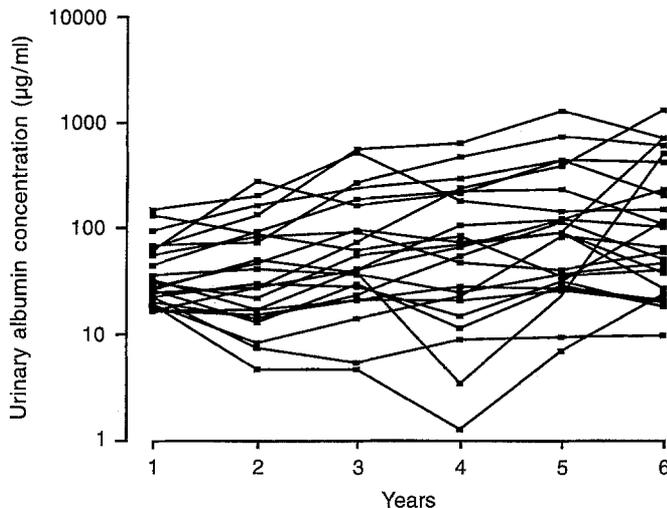


Fig. 3. Individual average annual albumin excretion in 24 patients with microalbuminuria during 6 years. On average UAC was increased from $36.4 \mu\text{g/ml} \times / \div 1.9$ to $96.9 \times / \div 4.0$, $p < 0.01$

Frequency

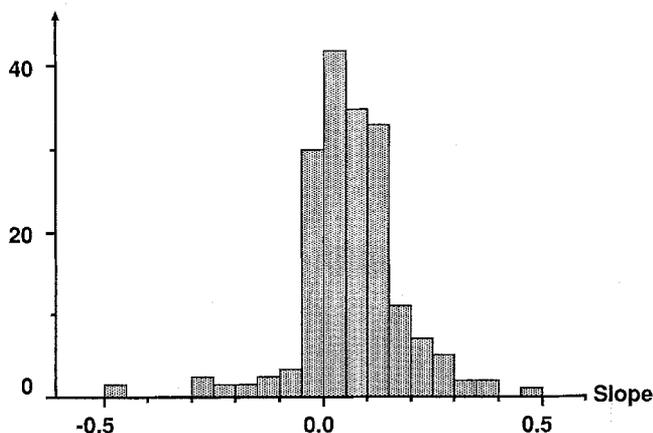


Fig. 4. Distribution of slope among patients with at least 4 years' follow-up. The overall increase was significantly different from zero $p < 0.0001$

all 6 years ($n = 135$), at least 4 years ($n = 178$), and more than 2 years ($n = 237$). The regression coefficients were 0.0694, 0.0697 and 0.0739, respectively, corresponding to annual increases in albuminuria of 17%, 17% and 19%. There was a rather large interindividual variation as demonstrated in Figure 4, which displays the distribution of slope among patients with at least 4 years' follow-up. Though tending to be slightly greater, the rate of increase in albuminuria did not significantly differ between patients with normal albumin excretion (16.4%) and microalbuminuria (23.3%) (in those with at least four years' follow-up figures were 17.2% and 24.5% respectively).

Which factors influence or associate with the rate of increase? Associations between clinical variables and the relative rate of increase appear in Table 4 for pa-

Table 4. Correlations between quantitative variables and albuminuria at baseline, average albuminuria and slope in patients with complete 6 year follow-up. Significant associations ($p < 0.05$) are indicated by bold figures

		Baseline albuminuria	Average	Slope
Age	(B)	0.009	0.004	0.189
Body mass index	(S)	0.077	0.050	-0.164
Plasma glucose	(B)	0.131	0.129	-0.083
	(S)	0.088	0.128	-0.007
	(A)	0.115	0.166	0.056
HbA _{1c}	(S)	0.224	0.263	0.071
Blood pressure				
systolic	(S)	0.127	0.221	0.258
diastolic	(S)	0.072	0.140	0.136
Baseline albuminuria		1	0.890	-0.050
Average	(S)	0.890	1	0.305

Table 5. Multiple regression analyses in patients with at least 4 years and (complete) 6 years of follow-up, with slope as dependent variable

Variable	At least 4 years		6 years	
	reg. coeff.	p-value	reg. coeff.	p-value
Systolic blood pressure	0.00147	0.0012	0.00102	0.0090
Average UAC	0.0323	0.018	0.0421	0.0013
Sex	-	0.18	-	0.92
Age	-	0.78	-	0.19
Body mass index	-	0.09	-0.0048	0.015
R ²	0.115		0.174	

reg. coeff.: regression coefficient

tients with complete 6-year follow-up. Slope was significantly associated with age, systolic blood pressure and average albuminuria. For patients with at least 4 years of follow-up, slope correlated with systolic ($r = 0.291$) and diastolic blood pressure ($r = 0.226$) and average ($r = 0.237$). Multiple regression analyses, Table 5, showed that systolic blood pressure and average UAC were the only variables remaining with a significant influence on slope in both categories. As it appears, the percentage of the variation explained by these variables (R^2) was modest.

Concerning antihypertensive medication, patients receiving this therapy and higher blood pressure (164/89 mmHg vs 155/85, $p < 0.01$, but the relationship between blood pressure and slope was independent of whether or not the patients were medicated. Also, number of years of follow-up or mode of anti-diabetic treatment were without any significant influence.

Among patients followed for at least 4 years, 46 progressed, Table 6. The average slope was 48%. Progressors had higher systolic blood pressure

Table 6. Number and percent of patients characterised as progressors in the group with at least 4 years of follow-up

		Albuminuria	
		Baseline	End
N → M	<i>n</i> = 34 ≈ 25 %	7.3 × / ± 1.8	28.4 × / ± 1.9
M → P	<i>n</i> = 11 ≈ 32 %	47.3 × / ± 2.0	499.0 × / ± 1.9
N → P	<i>n</i> = 1	3.0	1051.9
M → N	<i>n</i> = 3 ≈ 9 %	30.9	12.3
P → M	<i>n</i> = 1	446.4	87.0
P → N	<i>n</i> = 1	505.6	16.7

Last three rows include the five regressing patients. Albuminuria is given at baseline and at end of follow-up. N, Normal albumin excretion; M, microalbuminuria; P, proteinuria. Average UAC µg/ml

(165 mm Hg ± 20 vs 156 ± 17), $p < 0.01$, and poorer glycaemic control (HbA_{1C}: 8.2 % ± 1.5 vs 7.7 ± 1.3), $p < 0.05$, as compared to their non-progressing counterparts. They were similar in age (65.0 years ± 5.0 vs 63.4 ± 5.4) and diastolic blood pressure (89 mm Hg ± 8 vs 86 ± 9) was not significantly different. Albuminuria at baseline was elevated: 11.2 µg/ml × / ± 2.7 (range 1.2–140) vs 5.6 × / ± 2.9 (1–149), $p < 0.001$. Those with normal albumin excretion had values of 7.1 µg/ml × / ± 1.8 vs 3.8 × / ± 1.9, $p < 0.0001$, but the ranges were similar 1.2–14.9 µg/ml and 1–14.5 µg/ml. A total of five patients regressed; three from microalbuminuria to normal UAC, and two with proteinuria to microalbuminuria and normal albumin excretion, respectively.

A total of 80 patients died: 24 % of those with normal albumin excretion, 35 % of microalbuminuric patients and 60 % of patients with proteinuria. Those who died were older (65.7 years ± 4.2 vs 63.3 ± 5.4 $p < 0.001$) and had a higher albumin excretion both at baseline 16.8 µg/ml × / ± 6.4 vs 7.6 × / ± 3.9 ($p < 0.001$) and on average ($p < 0.01$), as compared to the remainder. The slope was, however, not significantly different among those who died (20.6 %) or survived (17.6 %).

The patients who did not complete the study were, apart from being slightly younger, no different with regard to any of the clinical parameters, as compared to the remainder: age: 62.6 years ± 5.4 vs 64.4 ± 5.1, $p < 0.05$; duration of diabetes: 8.4 years ± 6.2 vs 7.7 ± 5.9, BMI: 29.3 kg/m² ± 7.2 vs 28.3 ± 4.6; plasma glucose at baseline: 9.1 mmol/l ± 2.3 vs 9.3 ± 2.4; study period: 9.6 mmol/l ± 2.1 vs 9.6 ± 2.3; all: 8.9 mmol/l ± 2.1 vs 9.0 ± 1.8; HbA_{1C}: 7.7 % ± 1.8 vs 7.9 ± 1.2; systolic blood pressure: 154 mm Hg ± 18 vs 158 ± 21; diastolic blood pressure: 86 mm Hg ± 10 vs 87 ± 10; urinary albumin 85: 9.6 µg/ml × / ± 4.9 vs 9.6 × / ± 4.8.

Discussion

In the present study, the average relative rate of increase of albuminuria amounted to 17 % per year and our results point to two variables with positive association to this increase: systolic blood pressure and level of albuminuria.

Slope generally showed a marked interindividual variation, only a modest percentage of which could be explained by the variables analysed. Albumin excretion was assessed by concentrations in first morning urine samples, rather than in standardised timed collections, but the former is a valid estimate of UAE. Increased early morning UAC predicts raised UAE with a sensitivity of approximately 90 % and is well correlated to UAE [24–26]. A former longitudinal study demonstrated a conspicuous intraindividual variability during the evolution of albuminuria [27], and the day-to-day variation is known to amount up to 40–50 % [28]. In the present study, slope was estimated from yearly average based on several measurements. The population of NIDDM patients is probably a mosaic of those who eventually do develop complications and those who do not, as is the case in IDDM. In a former study we observed that a substantial number of similar patients remained normoalbuminuric over 10–13 years [6]. Among present participants 46 were defined as progressors, corresponding to 27 % of the eligible population (172 non-proteinuric patients with at least 4 years of follow-up). Progressors were characterised by elevated systolic blood pressure, higher level of albuminuria and poorer glycaemic control. Even though average baseline albuminuria was also increased among normoalbuminuric progressors, the lowest value was 1.2 µg/ml; serial measurements thus being mandatory for identifying such patients.

The results concerning evolution in albuminuria are difficult to compare to previous studies, which have been based mainly on two-point analyses in both types of diabetes. The annual increase in albuminuria in IDDM patients with incipient nephropathy followed for 5 years was 18 % [29], and in 13 patients characterised by progression from normo- to microalbuminuria 38 % per year during 9–14 years [30]. Even less data are available in NIDDM. A 10-year follow-up study [31] demonstrated that 20 % of patients with microalbuminuria will develop proteinuria over a decade, and nine NIDDM patients progressing as above showed a rate of increase of 42 % per year [30]. Cooper et al. [32] followed 61 NIDDM patients, 12 of whom were identified as progressing over a mean of 7 years. In contrast to the present finding there were no statistically significant differences in either blood pressure or glycaemic control between groups. This may be due to the smaller size of that population.

The higher rate of progression among patients with higher albumin excretion but no significant difference in slope among the albuminuria groups may seem to be contradictory. The division of patients in three groups is, however, arbitrary and based upon measurements at baseline; the latter will thus be subject to "regression towards the mean" effects. Average and slope are independent within patients and therefore uninfluenced by this phenomenon.

The longitudinal study of elderly people with NIDDM is inevitably compromised by the high frequency of disability and mortality and the selective influence of risk factors, among them elevated albuminuria. Also in our study a substantial number of patients died (29%) or were unable or unwilling to continue (22%). This leaves the 6-year cohort as a selected population. Overall, however, the results in the three subgroups were similar, though the patients with few years of follow-up did not add to the prospective results, apart from introducing more variation.

Glycaemic control has been shown to be important with regard to the development of diabetic microvascular complications [33–38], whereas its influence on macrovascular disabilities so far is doubtful [39–42]. As in previous studies glycaemic control was poorer in those with elevated albuminuria [1], but was without influence on slope. Gilbert et al. [30] reported a significant association between rate of change in UAE and HbA_{1c} in progressors, but whether this was due to those with poor control having a higher average is unclear. Optimising glycaemic control reduces albuminuria at least in short-term studies [12, 15–16], but the long-term consequences of such intervention are unknown in NIDDM patients.

In NIDDM the relation between systolic blood pressure and progression of albuminuria in our view is noticeable. In IDDM both systolic and diastolic blood pressure are associated with albuminuria, and with development of incipient and overt nephropathy blood pressures rise steadily [3, 29, 43, 44]. Anti-hypertensive therapy reduces albuminuria and retards the decline in kidney function [3, 29, 43–47]. Earlier we demonstrated that systolic blood pressure was related to the moderate rate of decline in kidney function in NIDDM patients with normo- or microalbuminuria [48]. A similar finding was reported by Gall et al. [49] in patients with proteinuria. In NIDDM several cross-sectional studies reveal that systolic blood pressure relates to albuminuria, whereas the connection with diastolic pressure is modest [1, 6–8, 13, 50–52]. Systolic blood pressure (also isolated systolic hypertension) appears to be the predominant associate with cardiovascular disease [1, 51, 53]. Albuminuria in NIDDM may reflect general vascular disease rather than merely diabetic glomerulopathy [1, 54].

In agreement with the consistent inference in previous studies, those patients who died had shown enhanced albumin excretion. The main causes of death are known to relate to cardiovascular disease. The relationship between increased albuminuria and a poor prognosis is yet not understood, and has not been explained by any known risk factors either alone or in combination. There are several studies to indicate that antihypertensive therapy may be beneficial as albuminuria is reduced [55–57] and possibly renal function can be preserved and possibly renal function can be preserved in NIDDM [58] as it is in IDDM.

The present study also points to blood pressure, besides albuminuria, as candidates for intervention. However, the interindividual variation in rate of progression of albuminuria is far from being explained by these factors alone. Whether therapy directed against them will improve survival or renal and cardiovascular morbidity is so far unknown, necessitating long-term studies. Furthermore other explaining factors are desired.

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