Albuminuria and 24-h Ambulatory Blood Pressure in Normoalbuminuric and Microalbuminuric NIDDM Patients

A longitudinal study

SØREN NIELSEN, MD
ANITA SCHMITZ, MD
PER L. POULSEN, MD
KLAVS W. HANSEN, MD
CARL E. MOGENSEN, MD

OBJECTIVE — To assess the long-term relationships between 24-h ambulatory blood pressure (AMBP), urinary albumin excretion (UAE) rate, and metabolic control in non-insulin-dependent diabetes mellitus (NIDDM) patients with normo- and microalbuminuria.

RESEARCH DESIGN AND METHODS — We conducted a prospective study of 23 NIDDM patients (11 with normoalbuminuria and 12 with microalbuminuria) receiving standard clinical care, including antihypertensive treatment, attending the outpatient clinic and 8 healthy control subjects. Twenty-four–hour AMBP and UAE were measured synchronously in addition to fasting plasma glucose, HbA_{1c}, and serum creatinine at baseline and after 4.6 (4.2–5.1) years [mean (range)].

RESULTS — Baseline systolic, but not diastolic, 24-h AMBP was significantly higher in diabetic patients compared with control subjects (146/80 [16/11] vs. 133/78 [9/9] mmHg, $P < 0.05$), but was similar in normoalbuminuric (143/81 [11/11] mmHg) and microalbuminuric (148/80 [20/10] mmHg) patients during strict blood pressure control. The annual increase in 24-h AMBP was equivalent in diabetic patients (0.6/−0.2 [2.6/1.5] mmHg/year) and control subjects (0.7/0.2 [1.2/1.4] mmHg/year, NS) and not significantly different from zero. Overall UAE did not change in control subjects (5.6 [1.6] vs. 4.4 [1.9]) (geometric mean [antilog SD]) or in the normoalbuminuric (8.7 [1.7] vs. 11.3 [3.0] μg/min) and microalbuminuric (35.7 [2.1] vs. 34.5 [3.2] μg/min) patients. In diabetic patients, the annual change in UAE correlated significantly with the annual change in the systolic ($r = 0.61$, $P < 0.002$) and diastolic ($r = 0.54$, $P < 0.008$) 24-h AMBP. In microalbuminuric patients, only the annual increase in systolic 24-h AMBP correlated significantly with the annual change in UAE ($r = 0.71$, $P = 0.010$), whereas in the normoalbuminuric patients, only the annual increase in diastolic 24-h AMBP and the annual change in UAE were significantly correlated ($r = 0.66$, $P = 0.026$). In a stepwise multiple linear regression analysis, the annual progression in albuminuria in NIDDM patients was significantly determined by increases in systolic (parameter estimate 0.018, SE 0.006, $P < 0.008$) as well as in diastolic 24-h AMBP (parameter estimate 0.026, SE 0.011, $P < 0.033$).

CONCLUSIONS — In an outpatient clinical setting, 24-h AMBP is similar in NIDDM patients with normo- and microalbuminuria. Alterations in both 24-h AMBP and UAE are on average moderate and equivalent compared with those in healthy control subjects. Although the average change in albuminuria is small, a progression in albuminuria relates to increments in both systolic and diastolic 24-h AMBP.

From Medical Department M (Endocrinology and Diabetes), Aarhus Kommunehospital, Aarhus, Denmark.
Address correspondence and reprint requests to Søren Nielsen, MD, Medical Department M (Endocrinology and Diabetes), Aarhus Kommunehospital, DK-8000, Aarhus, Denmark. E-mail: sn@endocrine.aau.dk.
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AMBP, ambulatory blood pressure; ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; NIDDM, non-insulin-dependent diabetes mellitus; UAE, urinary albumin excretion.

During recent years, even slight elevations in urinary albumin excretion (UAE) (so-called microalbuminuria) have emerged as a valid marker of premature morbidity and mortality from cardiovascular causes in non-insulin dependent diabetes mellitus (NIDDM) (1–6) and have been found to predict an increased incidence of overt diabetic nephropathy (1). Elevated albuminuria is a common feature of NIDDM and is often found at the time of diagnosis (7–12). Established cardiovascular risk factors such as arterial hypertension and dyslipidemia are frequently associated with NIDDM, maybe as aspects of common pathophysiological mechanisms (13) and as additional independent risk markers aggravating the risk of cardiovascular events already present in patients with NIDDM (14–17).

Studies comparing risk factors in normo- and microalbuminuric NIDDM patients have not shown clear differences in lipoprotein concentrations (18–21), but a tendency toward a more atherogenic lipid profile has been described in some microalbuminuric patients (21). Some studies, but not all, have found higher blood pressure (BP) levels in microalbuminuric patients, but based on measurements of 24-h ambulatory BP (AMBP) recordings, this difference may not be clear (22).

Little is known about the long-term changes in and interrelations between 24-h AMBP, UAE, and metabolic control in NIDDM. We therefore conducted a prospective study using synchronous measurements of 24-h AMBP and UAE in addition to metabolic control parameters in a previously described cohort of healthy subjects and NIDDM patients (receiving standard medical care) with normo- and microalbuminuria (22). The primary object of the study was to test whether a relation between the long-term alterations in BP and albuminuria in NIDDM patients could be detected by the use of simultaneous 24-h measurements. Secondary objectives were to compare

changes in 24-h AMBP and albuminuria in NIDDM patients with normo- and microalbuminuria with matched healthy control subjects.

RESEARCH DESIGN AND METHODS

— There were 32 NIDDM outpatients and 10 healthy control subjects initially studied during 1988–1989 who participated in this prospective observational study. Primary selection criteria were age 50–70 years and treatment of diabetes with diet alone or diet and oral agents (22). All subjects had normal serum creatinine and were without clinical cardiac insufficiency or major diseases unrelated to diabetes. Initially, patients were recruited on the basis of prevalent screening program values of urinary albumin concentration in the first morning urine sample. The actual UAE level was thereafter assessed from the mean of at least two 24-h urine collections. Recruitment was performed without knowledge of actual BP level or ongoing antihypertensive therapy. Fifteen patients were normoalbuminuric (defined as UAE <15 μg/min), and 17 had microalbuminuria (UAE from 15 to 200 μg/min). The diabetic groups and control subjects were matched for age, sex, body mass index (BMI), and diabetes duration (diabetes patients only). From the normoalbuminuric group, one patient refused to participate and three died. Among the microalbuminuric patients, one patient refused reinvestigation, one patient was disabled because of severe cerebral thrombosis, and three patients died. From the control group, two patients refused participation. A total of 23 diabetic patients (11 normoalbuminuric and 12 microalbuminuric) and 8 control subjects were reexamined after a mean observation period of 4.6 years (range 4.2–5.1). During the follow-up, three monthly controls were performed in the outpatient clinic, including antihypertensive treatment.

Blood samples were drawn after an overnight fast. Plasma glucose was measured by a glucose oxidase technique. Two different high-performance liquid chromatographic methods for HbA_{1c} measurement were used at baseline (23) and at follow-up (24). The interassay coefficients of variation were 5 and 2%, respectively. Plasma C-peptide was assessed by a radioimmunoassay kit (Immunonuclear, Stillwater, MN). Measurements of serum total cholesterol by continuous-flow analysis (25), serum triglycerides by an enzymatic technique (26), and serum creatinine by a modified Jaffe's reaction (27) were all adapted to the Technicon CHEM 1(R) analyzer. BMI was calculated as weight (kg)/height^2 (m^2) and used as an index of overall obesity.

Twenty-four–hour AMBP was measured by a portable automatic BP monitor (model 90202, SpaceLabs, Redmond, WA) using oscillometry (28). The device was programmed to measure BP every 20 min between 6:00 A.M. and midnight and every hour during the night. Patients recorded actual time for going to bed and rising in the morning for accurate appraisal of day and night BPs. Patients exhibiting a reduction in both nighttime systolic and diastolic BP of ≥10% compared with daytime values were defined as "dippers" (29). Three auscultatory measurements were performed after a 10-min rest in the sitting position using a random zero sphygmomanometer (Hawksley, Lancing, U.K.) using Korotkoff phase V as the diastolic value. The mean of such three measurements is termed the clinic auscultatory BP. Synchronously with the 24-h AMBP, one 24-h urine collection was obtained for determining UAE by radioimmunoassay (30). Urinary sterility was checked by a dipstick method (Multistix 8 SG, Ames, Bayer). The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from all patients participating in the study.

Statistical analysis

Values are presented as means (SD or range) or as medians (25th–75th percentile or range). Values expressing annual changes are given as the mean (95% confidence interval). UAE was log-transformed because of the positively skewed distribution and therefore given as the geometric mean (×/÷ antilog SD). The change in albuminuria was calculated from the ratio (follow-up value/baseline value), and after log transformation of this ratio, the annual relative change (expressed as ratio/year) could be calculated. Comparisons between all three groups were performed using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, and pairwise comparisons (corrected for multiple comparisons) were assessed by the Student-Neuman-Keuls test or Dunn's test. Comparisons between normo- and microalbuminuric patients and between diabetic patients and control subjects were analyzed by the Student's t test and the Mann-Whitney two-sample test. Fisher's exact test and the χ^2 test were used for analysis of noncontinuous variables. Multiple regression analysis was performed by stepwise linear regression analysis. Correlations were evaluated by Pearson's r analysis. $P < 0.05$ was considered statistically significant.

Power analysis

The power of Pearson's correlation analysis (expected r value >0.50, $\alpha = 0.05$) for the number of diabetic patients investigated ($n = 23$) is 79%. Student's t test comparisons of diabetic patients ($n = 23$) and control subjects ($n = 8$) with an expected difference between the two groups in the mean (SD) change in systolic and diastolic BP of 3 (2.5) and 2 (1.5) mmHg/year hold powers of 81 and 88%, respectively. Using the same figures for comparison of normo- and microalbuminuric patients results in a power of 78% for the systolic and 86% for the diastolic BP changes, respectively. Moreover, comparison of changes in albuminuria between diabetic patients and control subjects [expected difference in the mean (SD) log-transformed ratio/year of 0.1: log (1.200)] between groups holds a statistical power

Table 1—*Patient data*

	Normoalbuminuria	Microalbuminuria	Control
Age (years)	63 (6)	64 (6)	64 (3)
Sex (men/women)	6/5	9/3	6/2
Known diabetes duration (years)	6.1 (3.3)	6.4 (4.8)	—
BMI (kg/m^2)	27.9 (3.8)	30.7 (5.9)	26.6 (3.4)
Serum creatinine (μmol/l)	88 (12)	92 (11)	92 (11)
UAE (μg/min)	7.2 (1.5)	37.2 (2.1)	NM
Retinopathy (normal/background/ proliferative)	8/2/1	8/3/1	—
Antidiabetic treatment (diet/tablets)	1/10	2/10	—
Antihypertensive treatment (yes/no)	6/5	6/6	0/8

Data are means (SD). UAE values are geometric means (×/÷ antilog SD). UAE levels were obtained during recruitment of the patients and assessed as the mean of at least two 24-h urine collections. NM, not measured.

of 84% and, using the same figures for the comparison of normo- and microalbuminuric patients, holds a power of 82%.

RESULTS — Table 1 shows the baseline characteristics of the patients and control subjects attending the follow-up examination. Compared with the reexamined diabetic patients, the four normoalbuminuric and five microalbuminuric patients lost at follow-up had similar baseline levels of UAE (range: 3.5–9.0 and 17.1–69.0 μg/min); 24-h AMBP (median [range]: 141 [128–149]/77 [70–92] mmHg [three nondippers] and 139 [121–162]/79 [67–91] mmHg [two nondippers], normo- and microalbuminuric patients, respectively). Furthermore, as determined from hospital records and death certificates, none of these patients had developed uncontrolled hypertension, proteinuria (UAE >200 μg/min), or end-stage renal failure. The individual drugs used for blood pressure control are listed in Table 2. Thus, antihypertensive therapy was initiated or increased during the follow-up in seven normoalbuminuric (A.G., E.H., K.N., R.M., I.O., H.R., and J.L.) and six microalbuminuric patients (E.B., O.C., P.E., G.H., I.E., and E.S.), while one control subject (W.F.) started antihypertensive therapy during the study.

Glycemic control was unaltered during the study, as shown in Table 3. Baseline systolic, but not diastolic, 24-h AMBP was significantly higher in diabetic patients compared with control subjects (146/80 [16/11] vs. 133/78 [9/9] mmHg, $P < 0.05$ for systolic values), but similar in normo- and microalbuminuric patients

Table 2—*Drugs used for blood pressure control at baseline and follow-up*

Patient	Baseline	Follow-up
A.G. (N)	0	Calcium channel blocker
E.H. (N)	0	Amiloride/thiazide
K.N. (N)	0	ACE inhibitor
R.M. (N)	0	ACE inhibitor
J.J. (N)	Thiazide	Loop diuretic (UP)
I.O. (N)	Amiloride/thiazide	Amiloride/thiazide (UD) + calcium channel blocker
B.P. (N)	Loop diuretic	Thiazide (UP)
H.R. (N)	Loop diuretic	Thiazide + β-blocker
J.L. (N)	Loop diuretic + β-blocker	Loop diuretic (ID) + calcium channel blocker + ACE inhibitor
E.A. (N)	Loop diuretic + β-blocker	0
E.B. (M)	0	ACE inhibitor
O.C. (M)	0	ACE inhibitor
P.E. (M)	0	ACE inhibitor
O.P.C. (M)	Thiazide	Thiazide (UD)
G.H. (M)	Thiazide	Calcium channel blocker (IP)
I.E. (M)	Thiazide	ACE inhibitor (IP)
A.N. (M)	Loop diuretic + β-blocker	Loop diuretic (UD) + β-blocker (UD)
E.S. (M)	β-blocker + calcium channel blocker	β-blocker (ID) + calcium channel blocker (RD) + thiazide
V.A. (M)	ACE inhibitor	ACE inhibitor (UD)
W.F. (C)	0	β-blocker

N, normoalbuminuria; M, microalbuminuria; C, control; ACE, angiotensin-converting enzyme; UP, unchanged potency; IP, increased potency; UD, unchanged dose; ID, increased dose; RD, reduced dose compared to baseline.

Table 3—*Metabolic control parameters*

	Normoalbuminuria		Microalbuminuria		Control	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Fasting plasma glucose (mmol/l)	9.5 (2.8)	10.6 (3.3)	9.3 (3.2)	10.0 (3.6)	5.0 (0.8)*	6.4 (1.1)*
HbA_{1c} (%)	7.4 (0.6)	7.8 (1.4)	7.2 (1.4)	7.9 (1.5)	5.9 (0.6)*	6.1 (0.9)*
Serum C-peptide (μg/l)	2.6 (1.0)	1.9 (0.4)†	2.6 (1.2)	2.0 (0.5)†	2.1 (0.3)	1.7 (0.4)†
Total serum cholesterol (mmol/l)	NM	6.4 (1.2)	NM	6.6 (1.4)	NM	7.0 (1.1)
Serum high-density lipoprotein cholesterol (mmol/l)	NM	1.24 (0.22)	NM	1.41 (0.31)	NM	1.38 (0.36)
Serum triglycerides (mmol/l)	NM	1.63 (1.41–2.16)	NM	1.76 (1.17–2.85)	NM	1.59 (1.16–1.92)

Data are means (SD) or geometric means (×/÷ antilog SD). NM, not measured. *$P < 0.05$ control vs. normoalbuminuria, control vs. microalbuminuria (ANOVA); †$P < 0.05$ vs. baseline.

(143/81 [11/11] vs. 148/80 [20/10] mmHg, NS; the mean difference [95% confidence interval] for the systolic values was 0.6 [−9 to 20] mmHg). Both the systolic and the diastolic night-to-day ratios were comparable at baseline in the normoalbuminuric (0.94 [0.07] and 0.90 [0.12]) and microalbuminuric patients (0.89 [0.08] and 0.85 [0.07]) and in the control subjects (0.90 [0.07] and 0.88 [0.10], NS). The level of albuminuria was similar before and after follow-up in the normoalbuminuric (8.7 ×/÷ 1.7 vs. 11.3 ×/÷ 3.0 μg/min, NS) and microalbuminuric patients (35.7 ×/÷ 2.1 vs. 34.5 ×/÷ 3.2 μg/min, NS), as well as in the control subjects (5.6 ×/÷ 1.6 vs. 4.4 ×/÷ 1.9 μg/min, NS). The known diabetes duration at baseline was significantly longer in nondippers compared with dippers (8.5 [3.3] vs. 3.4 [3.0], $P < 0.02$), and significant correlations between the diabetes duration and both the systolic and the diastolic night-to-day ratio were noted ($r = 0.44$, $P < 0.05$ and $r = 0.60$, $P < 0.01$ for systolic and diastolic BP, respectively).

The overall as well as the annual increases in 24-h AMBP were equivalent in diabetic patients and control subjects and not significantly different from zero (Table 4). Clinical BP and 24-h AMBP were similar and not different between the three groups. Moreover, no alterations were observed in either daytime or nighttime BP. A reduction in the night-to-day ratio was observed in the control group, while stable values were found in both diabetic groups. The annual relative change in albuminuria was on average similar in all three groups but varied considerably between individuals, ranging from 0.600 to 1.451 ratio/year in the diabetic patients and from 0.808 to 1.133 ratio/year in the control subjects. In diabetic patients, albuminuria increased significantly in subjects taking no or a stable dose of antihypertensive therapy ($n = 9$) compared with that in those who initiated or increased such therapy during the follow-up ($n = 13$) (1.144 [0.999–1.310] ratio/year vs. 0.938 [0.839–1.048] ratio/year, $P = 0.020$). The concomitant change in the systolic 24-h AMBP was 1.4 (0.0–2.7) vs. 0.0 (−1.8–1.8) mmHg/year (NS) and in diastolic was 0.5 (−0.5–1.6) vs. −0.7 (−1.7–0.2) mmHg/year ($P = 0.064$). In one patient, antihypertensive medication was withdrawn because of the development of a normal BP level.

Changes in 24-h AMBP and albu-

Table 4—*Overall and calculated annual changes in 24-h AMBP, clinical BP, and UAE*

	Normoalbuminuria	Microalbuminuria	Control
24-h systolic BP (mmHg)	3.2 (−4.6–11.0)	2.6 (−5.6–10.8)	3.0 (−1.5–7.4)
24-h systolic BP (mmHg/year)	0.6 (−1.0–2.3)	0.6 (−1.2–2.3)	0.7 (−0.3–1.7)
24-h diastolic BP (mmHg)	−1.1 (−5.6–3.4)	−1.3 (−6.3–3.7)	0.7 (−4.5–5.9)
24-h diastolic BP (mmHg/year)	−0.2 (−1.2–0.7)	−0.2 (−1.3–0.8)	0.2 (−1.0–1.4)
Clinical systolic BP (mmHg)	2.9 (−8.0–13.8)	5.7 (−8.7–20.1)	6.0 (−2.7–14.7)
Clinical systolic BP (mmHg/year)	0.6 (−1.7–2.8)	1.3 (−1.8–4.3)	1.4 (−0.6–3.4)
Clinical diastolic BP (mmHg)	0.5 (−8.7–9.7)	2.3 (−6.5–11.2)	2.9 (−7.6–13.4)
Clinical diastolic BP (mmHg/year)	0.0 (−1.9–2.0)	0.5 (−1.3–2.4)	0.7 (−1.7–3.1)
UAE (ratio)	1.304 (0.767–2.220)	0.966 (0.488–1.912)	0.792 (0.501–1.252)
UAE (ratio/year)	1.056 (0.946–1.178)	0.990 (0.855–1.146)	0.948 (0.853–1.054)

Data are means (95% confidence interval) or geometric means (antilog 95% confidence interval).

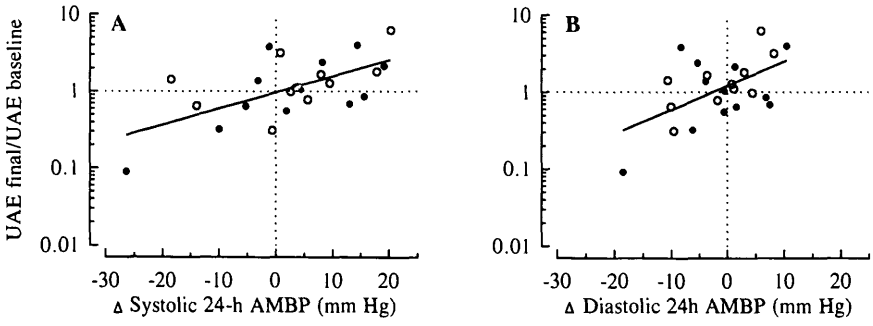

Figure 1—*Overall change in albuminuria as related to changes in 24-h systolic (A) (r = 0.61, P = 0.002) and diastolic (B) (r = 0.54, P = 0.008) AMBP in normo- (○) and microalbuminuric (●) NIDDM patients.*

minuria were similar in diabetic patients identified at baseline as dippers (n = 10) and nondippers (n = 13) (systolic: 0.8 [−1.1–2.6] vs. 0.5 [−1.1–2.1] mmHg/year, NS; diastolic: −0.1 [−1.0–0.8] vs. −0.3 [−1.4–0.7] mmHg/year, NS; change in albuminuria 0.993 [0.906–1.089] vs. 1.043 [0.900–1.209] ratio/year, NS). Moreover, similar values were obtained in diabetic patients without retinopathy (n = 16) and with retinopathy (simplex or proliferative) (n = 7) with regard to annual change in 24-h AMBP (systolic: 0.6 [−0.9–2.0] vs. 0.7 [−1.4–2.9] mmHg/year, NS; diastolic: −0.3 [−1.1–0.6] vs. −0.2 [−1.6–1.2] mmHg/year, NS) or relative change in albuminuria (0.983 [0.888–1.089] vs. 1.112 [0.920–1.345] ratio/year, NS). The prevalence of nondippers tended to be higher in patients with retinopathy (6 of 7) than in patients with a normal eye background (7 out of 16) (P = 0.089).

A significant correlation was observed between the overall changes in both the systolic and the diastolic 24-h AMBP and the overall change in UAE (Fig. 1). Figure 2 shows the relations after conversion of data to annual rates. In contrast, clinical BP measurements failed to pick up a significant correlation between the annual changes in diastolic BP and albuminuria (r = 0.37, P = 0.08). The relation between changes in clinic systolic BP and albuminuria was still significant (r = 0.43, P = 0.039), but was not as precise as with the change in 24-h AMBP. In microalbuminuric patients, increases in UAE and systolic 24-h AMBP correlated significantly (r = 0.71, P = 0.010), and a tendency was found in normoalbuminuric patients (r = 0.49, P = 0.11). Conversely, in normoalbuminuric patients, a significant correlation was found between increases in UAE and the diastolic 24-h AMBP (r = 0.66, P = 0.026), and a tendency was found in microalbuminuric patients (r = 0.46, P = 0.15). As seen from Figs. 1*A* and 2*A*, an increase in albuminuria (i.e., UAE ratio >1.0 or log [albumin ratio]/year >0.0) was rather uncommon, although barely significant, in patients with a reduction in systolic 24-h AMBP (P = 0.07, Fisher's exact test). No significant correlations were observed between the annual change in UAE and changes in metabolic control or in the baseline levels of UAE, 24-h AMBP, or metabolic control. Moreover, changes in 24-h AMBP and BMI were not significantly correlated. In a stepwise multiple linear regression analysis with the change in UAE as the dependent variable and with follow-up time, changes in HbA_{1c}, serum C-peptide, serum creatinine, and systolic and diastolic (entered separately) 24-h AMBP (or clinic BP) as independent variables, the annual progression in UAE in diabetic patients was significantly determined by increases in the systolic (parameter estimate 0.018, SE 0.006, P < 0.008) as well as in the diastolic 24-h AMBP (parameter estimate 0.026, SE 0.011, P < 0.033) (Table 5). In contrast, entering baseline levels of age, diabetes duration, 24-h AMBP (or clinic BP), BMI, UAE (calculated as the mean of baseline and follow-up values to avoid regression to the mean), serum creatinine, HbA_{1c}, serum C-peptide, systolic and diastolic night-to-day ratio, and treatment of diabetes as independent variables failed to pick up any significant predictors of the changes in UAE (data not shown).

CONCLUSIONS— This prospective study shows higher systolic 24-h AMBP values in normo- and microalbuminuric NIDDM patients receiving standard clinical care compared with those in healthy control subjects. Furthermore, we found that both systolic and diastolic 24-h AMBP, as well as the level of albuminuria, remained stable throughout the study pe-

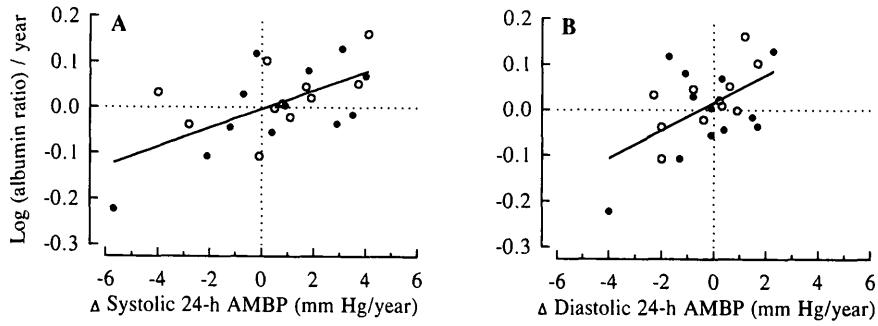

Figure 2—*Annual relative change in albuminuria as related to annual changes in 24-h systolic (A) (r = 0.61, P = 0.002) and diastolic (B) (r = 0.54, P = 0.008) AMBP in normo- (○) and microalbuminuric (●) NIDDM patients.*

Table 5—*Stepwise linear multiple regression analysis in NIDDM patients*

	Original model			Final model (Stepwise backward)		
Variable	Parameter estimate	SD	*P* value	Parameter estimate	SD	*P* value
Follow-up time	0.148	0.098	0.155	Eliminated	—	—
Rise in HbA_{1c}	0.083	0.063	0.210	Eliminated	—	—
Rise in serum C-peptide	0.121	0.088	0.192	Eliminated	—	—
Rise in serum creatinine	−0.004	0.006	0.435	Eliminated	—	—
Rise in systolic BP	0.017	0.006	0.017	0.018	0.006	0.008
Rise in diastolic BP	0.025	0.011	0.035	0.026	0.011	0.033

Dependent variable: annual rise in UAE.

riod. However, in diabetic patients, changes in the systolic as well as the diastolic 24-h AMBP were significantly related to changes in albuminuria.

The present study is the first that compares long-term alterations in 24-h AMBP and UAE in a synchronously collected 24-h urine sample in patients with established NIDDM. Clearly, our results should be interpreted cautiously, as the results from those patients who were lost during the follow-up are unavailable. This is a common problem in this type of study and may mask a selective mortality/drop out of those patients prone to the highest increases in BP and/or albuminuria and maybe also the patients with progressive structural renal lesions. In this study, baseline characteristics of the patients who were lost at follow-up were, however, not different from the rest and patient records and death certificates documented that none had developed overt proteinuria or uncontrolled hypertension. Moreover, any conclusions about a true linear change rate in BP and albuminuria are partly speculative because only two measurements were made in each patient.

The patients were investigated in an outpatient clinical setting, allowing antidiabetic and antihypertensive therapy to be currently adjusted. Previous studies have shown a positive correlation between systolic BP and albuminuria (6,11,22). Furthermore, the ability of antihypertensive therapy to reduce albuminuria, even in normotensive NIDDM patients, is well described (31–34). This was partly confirmed in our study because albuminuria increased significantly more in patients taking no or a stable dose of antihypertensive drugs in comparison with patients who initiated or increased such therapy. Indeed, systolic BP is related to alterations in kidney function in NIDDM (35–37). In a recent study (35), we showed that systolic BP predicted the future decline in the glomerular filtration rate (GFR) in NIDDM patients with normo- and microalbuminuria. This relation was also maintained when the analysis was confined to those patients (73%) not taking antihypertensive drugs. The change rate of GFR was not determined by the level of albuminuria, metabolic parameters, or baseline GFR. Similarly, Ravid et al. (36), in somewhat younger normotensive patients followed for 14 years, noted a relation between the rate of decline in renal function (estimated by the reciprocal serum creatinine) and elevations in systolic BP.

In the present study, we demonstrated a significant relation between alterations in diastolic BP and UAE. This is a new observation and may be the result of the combination of simultaneous measurements of BP and UAE in combination with a more precise estimation of daily life BP, rather than clinic BP measurements, which are partly influenced by the "white coat hypertension" phenomenon. The results were not influenced by differences in glycemic control and, based on the follow-up measurements, there was no indication of differences in lipoprotein concentrations.

Alterations in albuminuria were similar in patients with and without retinopathy. This is interesting in light of the findings of Parving et al. (38) who recently demonstrated that the absence of retinopathy in the presence of proteinuria suggests kidney disease of nondiabetic origin. Moreover, recent data from the same group indicate a more rapid decline in kidney function as well as a more pronounced increase in albuminuria in proteinuric NIDDM patients with biopsy-proven diabetic glomerulopathy compared with that in patients with nondiabetic glomerulopathy (39).

Very few patients exhibited a rise in albuminuria simultaneously with a reduction in the systolic BP (Figs. 1*A* and 2*A*). This has also recently been observed (only much more clearly) in insulin-dependent diabetic patients in the transition from normo- to microalbuminuria (40) and suggests that a rise in albuminuria is associated with an increase in systolic BP. These observations favor the notion that control of BP plays one key role in efforts to prevent an increase in albuminuria and further kidney damage. However, our data do not suggest that a rise in systolic BP triggers an increase in UAE. Thus, the relative role of hemodynamically determined alterations in albuminuria resulting from daily life perturbations in BP (i.e., functionally determined albuminuria) and structural kidney lesions influencing both BP and albumin-

uria (i.e., morphologically determined albuminuria) is difficult to reconcile. But obviously the BP and albuminuria fluctuate together.

More studies have shown a progressively abnormal diurnal variation in BP (i.e., impaired decline of nocturnal BP) with increasing levels of albuminuria in NIDDM (41–44), but so far the prognostic significance of an abnormal diurnal BP pattern is not known. We observed no difference between dippers and nondippers with regard to changes in BP or albuminuria, but nondippers had significantly longer diabetes durations. However, a multiple regression analysis revealed that neither diabetes duration nor the presence or absence of nondipping was related to alterations in albuminuria. It should be pointed out that antihypertensive treatment may disturb normal diurnal variation in blood pressure, which may result in misclassification of some of the patients. Therefore, failure of the night-to-day blood pressure ratio to explain changes in albuminuria cannot be extended to conclude that an abnormal diurnal untreated blood pressure variation is not a risk marker of alterations in UAE.

Recent observations indicate that commonly accepted cardiovascular risk factors also act independently in NIDDM (12,45), whereas the additive effects of hypertension and NIDDM on cardiovascular risk have been known for some years. So far, the effects of antihypertensive treatment on survival or the incidence of cardiovascular events in NIDDM are not known (46). Because abnormal albuminuria is also a strong cardiovascular risk marker, long-term studies focusing on concomitant changes in BP and albuminuria are of interest to clarify whether simultaneous alterations of the two occur, indicating a relationship (but not necessarily a cause-effect relationship), or whether one of the variables deteriorates independently of the other, suggesting that the influence of other factors may be involved. From this study, it is concluded that alterations in albuminuria may primarily be associated with fluctuations in BP and that normo- and microalbuminuric NIDDM patients in a clinical outpatient setting display rather stable values of BP and albuminuria during standard treatment. Moreover, our data suggest that an increase in albuminuria is accompanied by a rise in systolic BP. More studies, including serial measurements in a larger study population, are needed before any precise cause-effect relationship can be elucidated.

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