Relationship Between Blood Pressure and Urinary Albumin Excretion in Development of Microalbuminuria

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Two hundred nine consecutive normotensive insulin-dependent diabetic (IDDM) patients were followed prospectively from November 1982 to January 1988. Patient urinary albumin excretion rate (UAE) had to be normal (<30 mg/24 h) on at least two occasions before inclusion in the study. Patients were aged 18–50 yr with a duration of diabetes of 10–30 yr. UAE was measured every 4 mo, and supine blood pressure was measured annually. Two hundred five patients completed the study. Five years later, 15 patients had developed persistent microalbuminuria with median UAE >30 mg/24 h for at least 2 yr (group 2), and 190 patients stayed normoalbuminuric (group 1). Although within normal range, initial UAE was significantly elevated in group 2 compared with group 1 (mean 19 mg/24 h [range 15–23 mg/24 h] vs. 11 mg/24 h [10–12], 95% confidence interval [CI], $P < 0.001$). Initially, there was no difference in blood pressure between group 2 (mean systolic 122 mmHg [117–127], diastolic 80 mmHg [76–84]) and group 1 (mean 126 mmHg [124–128], 79 mmHg [78–80], 95% CI), and a significant increase in diastolic blood pressure could first be detected during the 3rd yr of persistent microalbuminuria (mean systolic 132 mmHg [124–140], diastolic 85 mmHg [81–89] vs. 128 mmHg [126–130], 79 mmHg [78–80], $P < 0.05$). Initial hemoglobin A_{1c} was significantly elevated in group 2 compared with group 1 (9.6% [8.8–10.4] vs. 8.5% [8.3–8.7], $P < 0.01$). Regarding sex, age, duration of diabetes, insulin dose, height, weight, or inverse serum creatinine, no significant differences were seen between the groups. No increase in UAE or blood pressure was detected in group 1, although 38% had experienced at least one elevated UAE during the 5-yr follow-up. Thus, a significant elevation in UAE precedes the increase of systemic blood pressure during the development of nephropathy in IDDM. *Diabetes* 39:245–49, 1990

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Clinical nephropathy in insulin-dependent diabetic (IDDM) patients is characterized by persistent albuminuria and elevated blood pressure (1,2). A phase with elevated urinary albumin excretion (UAE; 30–300 mg/24 h), so-called microalbuminuria, precedes the development of nephropathy in IDDM patients (3–6). Cross-sectional studies of IDDM patients with microalbuminuria have shown elevated blood pressure compared with IDDM patients with normal UAE (5,7), and prospective studies have demonstrated that the progression of microalbuminuria is associated with an increase in blood pressure (8). The close association between systemic blood pressure and microalbuminuria is supported by the fact that acute and long-term reduction of blood pressure in normotensive IDDM patients with microalbuminuria causes normalization of UAE (9,10). Which of these two variables preceded the other in the development of nephropathy has been debated. Recently, an increase in hypertension among parents of IDDM patients developing diabetic nephropathy has been reported, and a genetic predisposition to hypertension has been proposed as a factor in IDDM patients developing diabetic nephropathy (11,12). In this study, the hypothesis that an initial rise in blood pressure triggers the increased UAE was investigated by studying the time course of transition from normal UAE to microalbuminuria in IDDM patients.

RESEARCH DESIGN AND METHODS

Two hundred eleven IDDM patients with normal UAE were selected between October 1982 and January 1983. They fulfilled the following criteria: age 18–50 yr, onset of IDDM before age 30 yr, duration of diabetes 10–30 yr, regular attendance in the outpatient clinic at Steno Memorial Hospital, diastolic blood pressure <100 mmHg, sterile urine with normal urinary microscopy, and UAE <30 mg/24 h in one 24-h urine sample collected at home. None were taking any medications except insulin. During the 1st yr of observation, at least two of three UAE tests had to be within normal range

to secure an observation period with normoalbuminuria. Two hundred nine patients fulfilled this additional criterion.

To enroll and maintain enough patients and to minimize the study effect on the spontaneous course of blood pressure and UAE, study design was adapted to the routine in our clinic. Patients were followed prospectively in the diabetes clinic every 4th mo with UAE measurement in one 24-h urine sample collected at home. Annually, blood pressure, serum creatinine, and hemoglobin A_{1c} (HbA_{1c}) were measured, and urinary microscopy was performed. One 24-h urine sample was routinely obtained every 4 mo, but measurement of supine (10 min rest in a quiet room) blood pressure was restricted to once a year due to limitations in accommodation. Patient care, including blood pressure measurement, was continued by a diabetes-trained registrar to whom the patients were accustomed. Two hundred five patients (98%) completed the follow-up observation period for 5 yr until 1 January 1988.

Patients were grouped according to all UAE measured in the observation period (mean 13 tests/patient). Group 1 included patients with normoalbuminuria who did not fulfill the criteria for group 2. Group 2 included patients who developed persistent microalbuminuria defined as UAE >30 mg/24 h in at least two of three consecutive samples in 2 subsequent yr. The onset of persistent microalbuminuria was defined as the first elevated UAE included in the definition. Group 1 was subdivided into three groups (A–C) according to presence of occasional UAE >30 mg/24 h. Antihypertensive medication was initiated if blood pressure exceeded 160/95 mmHg on three consecutive occasions.

Albumin concentration was measured with a radial immunodiffusion technique with an interassay coefficient of variation (C.V.) 11.7%, sensitivity 3 mg/L (13). On 10 May 1985, the method was changed to an enzyme-linked immunosorbent assay technique, interassay C.V. 8.3%, sensitivity 0.001 mg/L (14). The correlation between the two methods was 0.99, $n = 80$ (14). The biological intraindividual day-to-day variation in the 24-h UAE was 40–50% in our clinic (15).

Blood pressure was recorded to the nearest 5 mmHg with a standard sphygmomanometer (cuff, 25 × 12 cm) on the right arm after a 10-min supine rest. The observer knew the patient but was not aware of the level of UAE.

HbA_{1c} was measured by a chromatographic technique (normal range 4.1–6.4%; 16). Serum creatinine was measured by a reaction-rate method modified to eliminate pseudocreatinines. The interassay C.V. was <2.5% (17). Inverse serum creatinine adjusted for weight was calculated for each subject (18). Retinopathy was assessed by direct ophthalmoscopy after pupillary dilation.

The distribution of UAE was normalized by logarithmic transformation before statistical analysis. Values are means with 95% CI or SD, except for UAE where geometric mean and 95% CI are given. Patients in group 1 (A–C) were compared by analysis of variance, and, when statistically significant differences were found, unpaired *t* tests were used for comparisons between groups. Correlations were calculated with stepwise multiple linear regressions analysis. The change of UAE with time was calculated including all measured variables in a linear model (after logarithmic transformation). Results were significant at $P < 0.05$ (two tailed).

RESULTS

Fifteen patients developed persistent microalbuminuria (group 2) in the observation period, and 190 patients remained normoalbuminuric (group 1). At the start of the study, the two groups were comparable regarding sex, duration of diabetes, insulin dose, inverse serum creatinine corrected for weight, and presence of retinopathy (Table 1). Although within normal range, UAE was higher in group 2 than in group 1, and the patients were younger. Blood pressure levels in both groups were at the same level (Table 1). Mean annual UAE and blood pressure were calculated for each patient. The year before the development of persistent microalbuminuria, UAE was significantly elevated compared with group 1 (mean 20 mg/24 h [range 14–29 mg/24 h] vs. 12 mg/24 h [11–14], 95% CI), and the UAE continued to increase ~40%/yr (Fig. 1). Blood pressure levels were similar in the two groups before the development of persistent albuminuria (mean systolic 125 mmHg [118–132], diastolic 80 mmHg [76–84] vs. 125 mmHg [123–127] and 79 mmHg [78–80], respectively, 95% CI), and a significantly elevated

TABLE 1
Initial clinical data on 15 insulin-dependent diabetic patients developing persistent microalbuminuria (group 2) and 190 patients with normoalbuminuria (group 1) during a 5-yr observation period

	Group 1	Group 2
n (F/M)	84/106	7/8
Age (yr)	34 ± 8	30 ± 8*
Duration of diabetes (yr)	17 ± 5	16 ± 4
Height (m)	173 ± 8	171 ± 12
Weight (kg)	70 ± 10	70 ± 11
Insulin dose (IU/kg)	0.61 ± 0.16	0.67 ± 0.25
UAE (mg/24 h)	11 (range 10–12)	19 (range 15–23)†
Hemoglobin A_{1c}	8.5 ± 1.2	9.6 ± 1.6‡
Systolic blood pressure (mmHg)	126 ± 13	122 ± 10
Diastolic blood pressure (mmHg)	79 ± 9	80 ± 8
Serum creatinine (μM)	82 ± 10	80 ± 10
Weight/serum creatinine (kg · μM^{-1})	0.86 ± 0.12	0.89 ± 0.13
Retinopathy	94/91/5	4/10/1

Values are means ± SD except for urinary albumin excretion (UAE), which has geometric mean (95% CI). Retinopathy was scored as none/background/proliferative retinopathy.
*$P = 0.04$, †$P = 10^{-4}$, ‡$P = 2 \times 10^{-3}$.

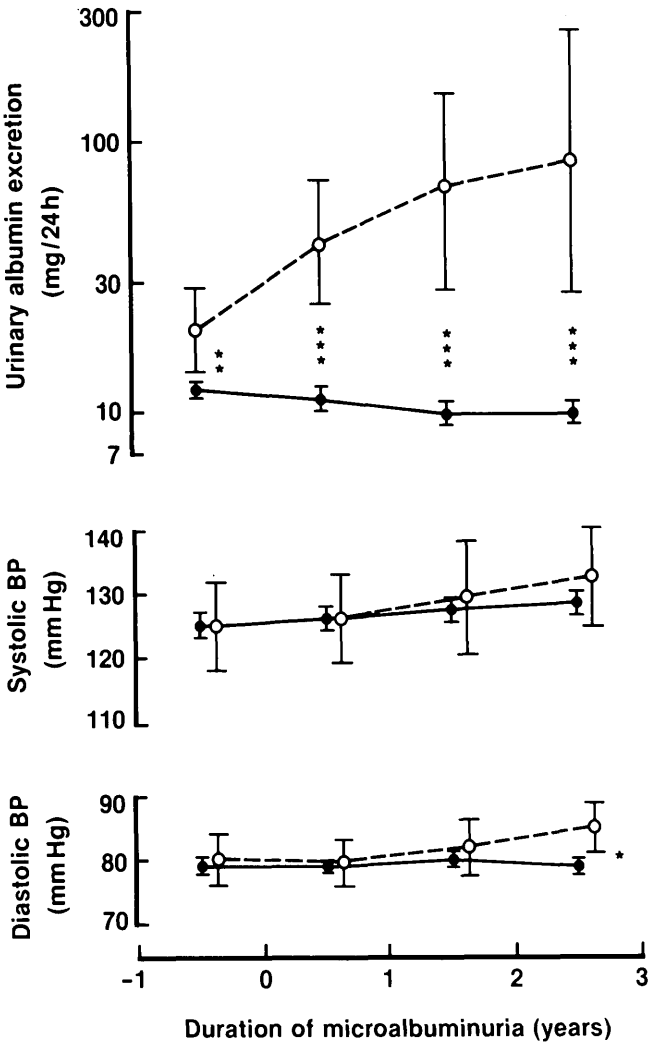

FIG. 1. Urinary albumin excretion and blood pressure (BP) in relation to duration of persistent microalbuminuria in 15 patients developing persistent microalbuminuria (○) compared with 190 patients who continue with normoalbuminuria (●). Mean and 95% confidence interval are given. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

diastolic blood pressure could first be detected during the 3rd yr of persistent microalbuminuria (mean systolic 132 mmHg [124–140], diastolic 85 mmHg [81–89] vs. 128 mmHg [126–130] and 79 mmHg [78–80], respectively; $P < 0.05$). During the follow-up period, 4 patients from group 1 and 1 patient in group 2 initiated antihypertensive treatment, and 10 patients from group 1 completed pregnancies.

In group 1, 118 (62%) patients had UAE <30 mg/24 h (group 1A), and 72 (38%) patients experienced at least one UAE in the microalbuminuric range during the 5-yr observation period. In 54 of the patients, a single elevated UAE occurred occasionally (group 1B), but as a consequence of the high day-to-day variation of UAE, 18 patients had two of three consecutive samples in the microalbuminuric range followed by UAE within normal range (group 1C). The normoalbuminuric patients who experienced occasionally elevated UAE had a higher initial UAE and HbA_{1c}, but the mean UAE did not increase during the observation period (Table 2). The initial and follow-up blood pressures were similar in the three subgroups, and none of the other variables showed any significant differences.

Long-term metabolic control, evaluated by initial HbA_{1c}, was poorer in patients later developing persistent microalbuminuria than in group 1 (Table 1). HbA_{1c} remained higher in group 2 than in group 1 throughout the study (mean ± SD HbA_{1c} 9.4 ± 1.5 vs. 8.3 ± 1.2%, $P < 0.01$). A multiple regression analysis with the last-measured UAE as the dependent variable was performed on all patients. Initial UAE ($P < 0.00001$) and HbA_{1c} ($P < 0.01$) had a significant influence on the UAE 5 yr later, whereas age, duration of diabetes, systolic and diastolic blood pressure, inverse serum creatinine corrected for weight, and degree of retinopathy were without significant influence.

During the follow-up observation period, serum creatinine was unchanged (group 1, mean ± SD 80 ± 9 μM; group 2, 81 ± 11 μM), and all individual serum creatinine values were within normal range. The initial prevalence of retinopathy (none/background/proliferative retinopathy) tended to be higher in group 2 (Table 1), and during follow-up 5 yr later, retinopathy progressed in patients with microalbuminuria, and prevalence of retinopathy was significantly higher compared with patients with normoalbuminuria (1/9/4 vs. 85/94/11, $P < 0.05$).

DISCUSSION

This prospective study is the first that evaluates the time course of the transition from normal UAE to persistent microalbuminuria (the initial phase in the development of diabetic nephropathy in IDDM patients). We found that a persistent increase in UAE precedes the increase of blood

TABLE 2
Initial and follow-up urinary albumin excretion (UAE) and blood pressure in normoalbuminuric patients

		UAE (mg/24 h)		Blood pressure (mmHg)		HbA_{1c} (%)	
	n	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up
Group 1A	118	10 (9–11)	8 (7–9)	$^{124 \pm 12}/_{78 \pm 8}$	$^{128 \pm 16}/_{78 \pm 9}$	8.3 ± 1.2	8.1 ± 1.2
Group 1B	54	12 (10–15)	12 (10–15)	$^{128 \pm 14}/_{80 \pm 9}$	$^{131 \pm 20}/_{79 \pm 10}$	9.0 ± 1.2*	8.6 ± 1.4*
Group 1C	18	15* (12–18)	15* (10–22)	$^{129 \pm 16}/_{82 \pm 10}$	$^{130 \pm 17}/_{81 \pm 9}$	8.5 ± 1.0	8.9 ± 1.0*

Values are means ± SD except for UAE in which geometric mean (95% confidence interval) is given. Values in parentheses are ranges. HbA_{1c}, hemoglobin A_{1c}. Group 1A, all UAE samples within normal range; group 1B, occasional single elevated UAE; group 1C, 2 of 3 elevated samples followed by UAE in normal range.
*$P < 0.05$ vs. group 1A.

pressure. Furthermore, one third of the normoalbuminuric diabetic patients experienced UAE in the microalbuminuric range during a 5-yr observation period without evidence of progression to persistent microalbuminuria.

Persistent microalbuminuria is observed in the initial phase of the development of diabetic nephropathy. A widely used definition of persistent microalbuminuria is UAE 30–300 mg/24 h in two of three consecutive urine samples (19). Because of the high day-to-day variation of UAE, some patients experience sporadic episodes of microalbuminuria without progressing to develop diabetic nephropathy (20). To exclude these patients, we included a 2-yr observation period in the above definition of persistent microalbuminuria. Fifteen patients developed persistent microalbuminuria between 1984 and 1986. This corresponds well with the 3% annual incidence of diabetic nephropathy (2).

The primary aim of this study was to test the time relationship between the early rise in UAE and blood pressure in the development of persistent proteinuria in IDDM patients. Many blood pressure measurements (total 1144) over several years in many patients were preferred to a high degree of precision in individual blood pressure recording. High variations in diastolic blood pressure from day to day (SD ± 7 mmHg) and from patient to patient (SD 10 mmHg) and a precision of 5 mmHg make a small increase in blood pressure (<4 mmHg) difficult to detect, but it is unlikely that a clinically significant increase in blood pressure (5 mmHg) before the development of microalbuminuria has been missed. Findings of no clinically significant difference in blood pressure the year before development of microalbuminuria are supported by the same results the year after development of microalbuminuria (Fig. 1). Thereafter, a slight gradual increase in diastolic blood pressure was demonstrated in patients with microalbuminuria. Antihypertensive treatment has a tremendous effect on UAE and, therefore, patients receiving antihypertensive treatment or having diastolic blood pressure >100 mmHg were not included in this study. In an unselected cross-sectional study, only 8% of patients with normoalbuminuria received antihypertensive treatment (21), and only 5 patients in this study initiated antihypertensive treatment during follow-up observations. Therefore, antihypertensive treatment probably did not bias the outcome of the study. Our findings suggest that the primary event in the development of persistent microalbuminuria is the affection of kidney function with secondary increases in systemic blood pressure. We do not support the hypothesis that a predisposition to essential hypertension results in an early increase in blood pressure that initiates the involvement of the kidney in the development of diabetic nephropathy (11,12).

In this study, the design and definition of persistent microalbuminuria excluded microalbuminuric patients with a spontaneous decline in UAE. This was probably the reason for the relatively steep annual increase of UAE by 40%/yr. At the beginning of the study, UAE was significantly elevated in group 2 compared with group 1. These tests were on average 2 yr before the development of persistent microalbuminuria in group 2. This finding suggests that UAE starts to increase several years before the development of persistent microalbuminuria. In this study, the observation period before the development of persistent microalbuminuria was too short to further illustrate the course of UAE before the development of persistent microalbuminuria.

Initially measured HbA_{1c} was independently correlated to UAE 5 yr later and was significantly higher in patients developing persistent microalbuminuria than in patients who continued with persistent normoalbuminuria. This finding is consistent with the finding of an association between poor metabolic control and the development of microalbuminuria in diabetic children (22,23). In our study, development of persistent microalbuminuria occurred only in patients with HbA_{1c} >7.5%, despite the fact that 25% of the study population had HbA_{1c} <7.5%.

One third of patients not developing persistent microalbuminuria experienced at least one UAE in the microalbuminuric range during the 5-yr follow-up period. Patients with normoalbuminuria were grouped according to presence of occasionally elevated UAE values (Table 2). Despite a tendency toward differences in UAE and blood pressure between subgroups, neither subgroup had any increase in UAE or blood pressure during the 5-yr observation period. This high prevalence of occasionally elevated UAE in diabetic patients not in the process of developing persistent microalbuminuria emphasizes the importance of taking several measurements of UAE before considering a patient to be at risk for developing diabetic nephropathy. In conclusion, this study demonstrates that increased blood pressure is secondary to the pathological processes in the kidney in IDDM patients developing persistent microalbuminuria.

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