Sodium Sensitivity Related to Albuminuria Appearing Before Hypertension in Type 2 Diabetic Patients

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OBJECTIVE — To find whether sodium sensitivity of blood pressure appears before hypertension and whether the sensitivity is related to diabetic nephropathy, we examined type 2 diabetic patients with normal levels of serum creatinine.

RESEARCH DESIGN AND METHODS — A total of 32 patients were divided into three age-matched groups: 11 patients had normoalbuminuria, 12 had microalbuminuria, and 9 had macroalbuminuria. Patients stayed on a diet with ordinary sodium levels for 1 week and a sodium-restricted diet for 1 week, in random order. Urinary excretion of sodium and albumin and systemic blood pressure were measured daily. A pressure-natriuresis curve was drawn by linkage of the two datum points obtained in the steady state during the different diets. We calculated the sodium sensitivity index as the reciprocal of the slope of this curve.

RESULTS — The median sodium sensitivity index and the mean blood pressure were higher in micro- and macroalbuminuric patients than in normoalbuminuric patients. Eighteen patients were without hypertension (<140/90 mmHg); of these, 10 had blood pressure readings <130/85 mmHg with ordinary sodium levels. Urinary albumin was correlated with the index but not with blood pressure. For these 10 patients, the index in those with albuminuria was higher than in those with normoalbuminuria. In such patients with albuminuria, sodium restriction decreased albuminuria and blood pressure.

CONCLUSIONS — In type 2 diabetic patients with albuminuria but normal levels of serum creatinine, sodium sensitivity of blood pressure appears before hypertension and is related to albuminuria; sodium restriction is one treatment for diabetic nephropathy, even without hypertension.

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Patients with renal disease, including diabetic nephropathy, come to have sodium-sensitive hypertension as renal dysfunction progresses because urinary sodium excretion decreases (1–3). It is not known when the increased sodium sensitivity of blood pressure appears. The objective of our study was to determine whether blood pressure in diabetic patients with early nephropathy is affected by sodium intake before hypertension appears. According to the standard classification of sodium sensitivity, when the mean arterial pressure (MAP) of a subject increases by ≥10% while on a diet with a high sodium level (250 mmol/day), as compared with a diet with a low sodium level (10 mmol/day), the blood pressure is considered to be sodium sensitive; if the MAP changes by <10%, blood pressure is considered to be sodium resistant (4,5). We decided not to use this classification because the change in blood pressure caused by the difference in sodium intake is a continuous variable. In addition, the cutoff levels for changes in blood pressure are arbitrary, as are the levels of sodium intake used in the studies (6–9), and the levels differ among studies.

Instead of using the protocol of earlier studies, we used the sodium sensitivity index (SSI) (the reciprocal of the slope of the pressure—natriuresis curve), which shows the sodium sensitivity of blood pressure independent of the magnitude of the change in sodium intake (2,10). We examined type 2 diabetic patients with early nephropathy to determine whether sodium sensitivity of blood pressure increases before hypertension begins and whether this sensitivity is related to albuminuria.

RESEARCH DESIGN AND METHODS

Patients

Our subjects comprised 32 inpatients with type 2 diabetes at Osaka City General Hospital. Patients were selected randomly and met the criteria of an expert committee (11). All had simple diabetic retinopathy. Patients with a history of nondiabetic renal disease, heart disease, or urinary tract infection or with serum creatinine of ≥97.4 μmol/l (1.1 mg/dl) or needing antihypertensive drugs were excluded. In all 32 patients, urinary sediment was free from red blood cells, and other indications of nondiabetic renal disease were lacking. All patients gave their informed consent, and the study was approved by an institutional ethical committee. The patients were divided into three groups by their level of albuminuria when the study was initiated (Table 1). For subjects on the regular hospital diet (~150 mmol of sodium/day), we defined urinary albumin excretion <20 μg/min (≤28.8 mg/24 h) as normoalbuminuria (n = 11); that of 20–200 μg/min

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Abbreviations: ANOVA, analysis of variance; MAP, mean arterial pressure; SSI, sodium sensitivity index; UNaV, urinary sodium excretion.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of diabetic patients at the start of the study*

	Patients with normoalbuminuria	Patients with microalbuminuria	Patients with macroalbuminuria
n	11	12	9
Sex (M/F)	5/6	7/5	7/2
Age (years)	61 ± 10	59 ± 10	62 ± 8
BMI (kg/m^2)	22.0 ± 2.1	24.4 ± 4.4	22.8 ± 4.3
Fasting plasma glucose (mmol/l)	6.81 ± 0.94	6.74 ± 0.71	7.19 ± 1.00
HbA_{1c} (%)	8.6 ± 1.1	8.1 ± 1.8	8.5 ± 1.6
Serum creatinine (mmol/l)	53.8 ± 13.9	60.4 ± 13.5	72.7 ± 16.4*
Systolic blood pressure (mmHg)	132 ± 11	136 ± 9	144 ± 8†
Diastolic blood pressure (mmHg)	73 ± 7	82 ± 6‡	85 ± 7§

Data are *n* or means ± SD. Normal HbA_{1c} values in our hospital are ≤5.8%. *P* values for ANOVA were calculated by Scheffe's test. **P* = 0.025; †*P* = 0.024; ‡*P* = 0.016; §*P* = 0.0012 vs. patients with normoalbuminuria.

(28.8–288 mg/24 h) as microalbuminuria (*n* = 12); and that >200 µg/min (≥288 mg/24 h) as macroalbuminuria (*n* = 9). Table 1 shows characteristics of the patients at the start of the study.

Study protocol

This study was performed after plasma glucose levels were brought under control during 2 or more weeks of hospitalization. The patients were then put on a diet with a low (~80 mmol/day) or ordinary (~200 mmol/day) sodium level for 1 week at each sodium intake level, in random order, with no time intervening. Two levels of sodium intake were used so that the pressure-natriuresis relationship could be investigated. The calories and the amount of protein provided to individual patients daily during the study were kept constant (30 kcal/kg and 1.2 g · kg^{-1} body wt · day^{-1}, respectively). Medications other than insulin or oral antihyperglycemic agents (sulfonylurea) were not administered. On each of the last 3 days of the diets, 24-h urine collection was performed, and the urine was assayed for concentrations of sodium, creatinine, and albumin. Sodium and albumin were assessed in terms of the means of these values. On the last day of each diet, a 24-h record of blood pressure was taken with a portable monitor by an oscillometric technique (Listmini, BP-8800; Colin, Aichi, Japan) with hourly measurements. The MAP was calculated by addition of one-third of the pulse pressure to the diastolic pressure, both of which were calculated as the means of values from the 24-h record. The renal clearance of creatinine and plasma renin activity were investigated simultaneously with the patients supine on the last day of each diet. On the last day of the diet with an ordinary sodium level, renal plasma flow was measured by the usual clearance method with *p*-aminohippurate.

Characterization of the pressure-natriuresis relationship and the SSI

Pressure-natriuresis curves were constructed by plotting of the urinary sodium excretion (UNaV) on the ordinate as a function of MAP on the abscissa (2,10). Assuming a linear relation between MAP and UNaV, a pressure-natriuresis curve for a patient can be drawn by linkage of two datum points obtained when the patient's sodium balance is in a steady state during the two diets with different amounts of sodium. Slope *B* (millimoles per day per millimeter of mercury) was calculated as follows (2):

$$B = \frac{U_{Na}V_O - U_{Na}V_L}{MAP_O - MAP_L}$$

where *O* and *L* denote results obtained in a steady state of sodium balance during a diet with an ordinary or low sodium level, respectively. (We calculated one mean UNaV for the last 3 days of each diet.)

The reciprocal of slope *B* reflects the sodium sensitivity of the blood pressure and therefore represents the SSI (2,12).

Statistical analysis

Most results are expressed as means ± SD. For plasma renin activity, urinary excretion of albumin, and the SSI, the values are expressed as medians with the 25th and 75th percentiles. The significance of differences between values for the characteristics of patients at the start of the study and for the SSI among the three groups of patients was evaluated by analysis of variance (ANOVA) with Scheffe's test and the Kruskal-Wallis test, respectively. Between the two groups of normotensive patients with normoalbuminuria or microalbuminuria, the significance of differences in parameters was evaluated by Student's *t* test for unpaired samples or the Mann-Whitney *U* test. The significance of differences during the two diets was examined with Student's *t* test for paired samples or Wilcoxon's signed-rank test. The correlation coefficients for urinary excretion of albumin on the diet with the ordinary sodium level with the SSI or MAP were calculated by the least-squares method. A difference with $P < 0.05$ was considered to be significant.

RESULTS — Figure 1*A* shows the relationship between the urinary excretion of sodium and MAP (the pressure-natriuresis curve) in the three groups of patients. The pressure-natriuresis curves of the patients with micro- or macroalbuminuria were shifted toward higher pressure levels with the slope less than the curve for patients with normoalbuminuria. The SSI in both groups of patients with albuminuria was higher than that for patients with normoalbuminuria.

With an ordinary level of sodium intake, 18 of 32 patients (8 of the 11 patients with normoalbuminuria, 8 of the 12 patients with microalbuminuria, and 2 of the 9 patients with macroalbuminuria) had normal systemic pressure (<140/90 mmHg). Among the 18 patients, 10 patients (6 of the 8 patients with normoalbuminuria, 3 of the 8 patients with microalbuminuria, and 1 of the 2 patients with macroalbuminuria) had systemic blood pressure of <130 mmHg systolic and <85 mmHg diastolic.

The pressure-natriuresis curves and SSI in these normotensive patients with normo- or microalbuminuria are given in Fig. 1*B*. The slope of the curve was less steep and the SSI was higher for patients with microalbuminuria than for patients with normoalbuminuria. Table 2 shows results for hemodynamics, plasma renin activity, and urinary excretion of albumin on the diets with low or ordinary sodium level for the 16 patients who were normotensive with normo- or microalbuminuria. In the patients with microalbuminuria, systemic blood pressure (both systolic and diastolic) and urinary excretion of albumin were decreased by the decrease in sodium intake.

Figure 1*C* shows pressure-natriuresis

curves and SSI in the patients with blood pressure at <130/85 mmHg on the diet with an ordinary sodium level. The slope of the curve was less steep and the SSI was higher for the patients with micro- or macroalbuminuria than for the patients with normoalbuminuria. In the patients with albuminuria (three with microalbuminuria and one with macroalbuminuria), systemic blood pressure (both systolic and diastolic) and urinary excretion of albumin were decreased by the decrease in sodium intake.

The correlations of urinary excretion of albumin with SSI and MAP in all patients studied are shown in Fig. 2*A* and *B*, respectively. (Values given for the urinary albumin excretion and MAP were obtained with patients on the diet with an ordinary sodium level.) Both correlations were significant. However, in the 18 patients without hypertension on the diet with an ordinary salt level, the albumin excretion was correlated with SSI (Fig. 2*C*) but not with MAP (Fig. 2*D*). In the 10 patients with a blood pressure of <130/85 mmHg, albumin excretion was significantly correlated with SSI ($r = 0.75$, $P = 0.010$) but not with MAP ($r = 0.49$, $P = 0.15$).

CONCLUSIONS — We found increased sodium sensitivity of blood pressure in type 2 diabetic patients with micro- or macroalbuminuria but without hypertension; the sensitivity was related to their nephropathy (albuminuria).

Hypertension in almost all patients with diabetes is sodium sensitive (2,8). Elevation of systemic blood pressure to the hypertensive level is an early and common phenomenon in diabetic nephropathy (3,13,14). The findings in Fig. 1*A* summarizing results from all 32 patients reflect both phenomena. However, hypertension is present at the time of diagnosis of type 2 diabetes, regardless of nephropathy, in approximately one-third of type 2 diabetic patients (15). Hypertension in type 2 diabetic patients may be related not only to underlying diabetic nephropathy but also to coexisting essential hypertension or other secondary causes (15). By excluding patients with hypertension (>140/90 mmHg), we investigated whether the sodium sensitivity of blood pressure was greater in diabetic patients with micro- or macroalbuminuria than in those with normoalbuminuria and found that it was. It is worth noting that the same results were obtained in patients with blood pressure measurements <130/85 mmHg.

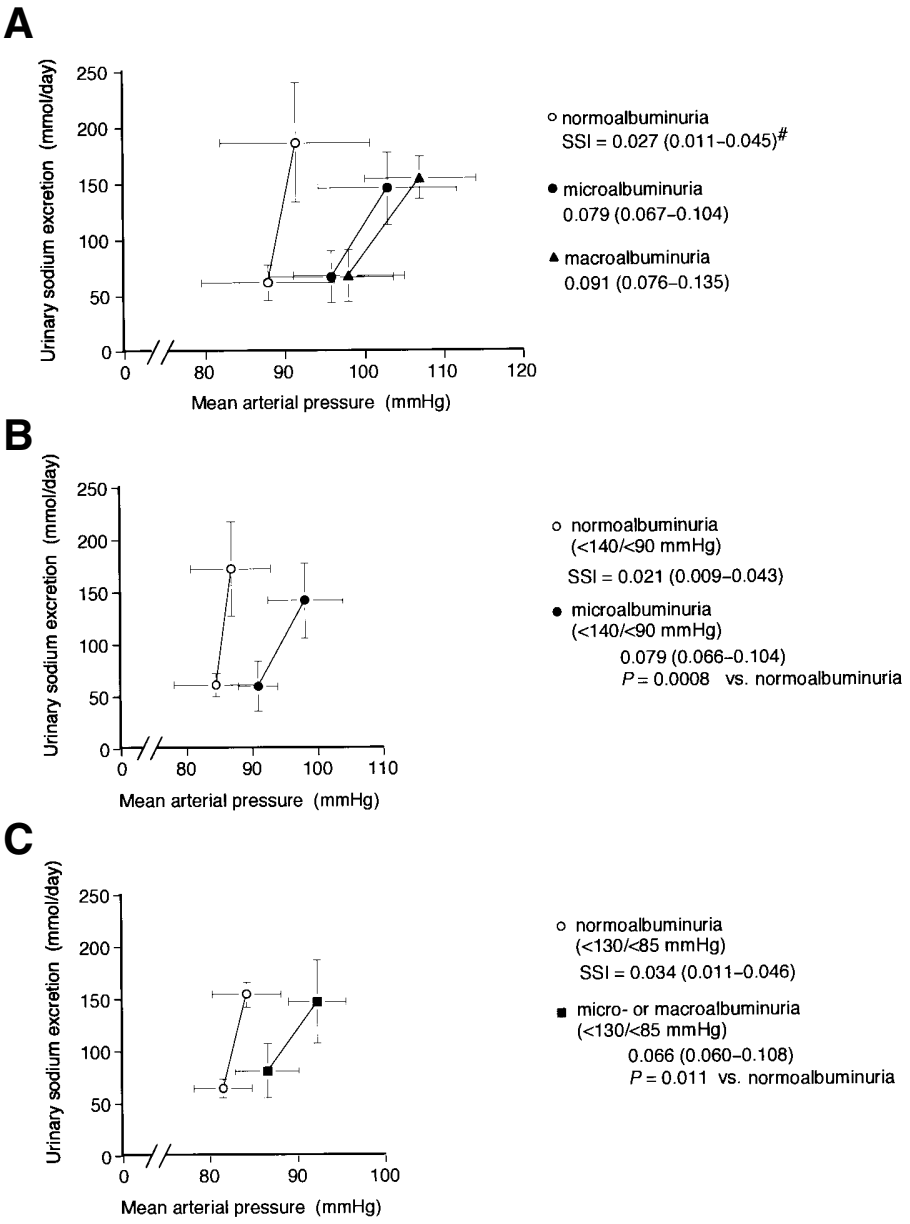

Figure 1—*Relationship between the urinary excretion of sodium and mean arterial pressure (pressure-natriuresis curve) in those with normoalbuminuria, microalbuminuria, or macroalbuminuria* (A)*; in the two groups of normotensive (<140/90 mmHg) patients with normoalbuminuria* (n = 8) *or microalbuminuria* (n = 8) (B)*; and in the two groups of truly normotensive (<130/85 mmHg) patients with normoalbuminuria* (n = 6) *or albuminuria (including micro- and macroalbuminuria)* (n = 4) (C)*. Values are means ± SD. The SSI is given as the median (25th to 75th percentile). #*P *< 0.001 vs. patients with micro- or macroalbuminuria, as measured with the Kruskal-Wallis test; all other* P *values for SSI are calculated with the Mann-Whitney* U *test.*

We matched patients in the three groups for age because a longitudinal study showed that sodium sensitivity of blood pressure increases with increasing age, especially in hypertensive subjects (16).

The pressure-natriuresis curve within the experimental range of sodium intake is linear for experimental animals and humans with normotension or hypertension (10). This curve is linear for individual patients with a daily sodium intake of 1–18 g NaCl (18–308 mmol sodium) (17). Within this range of sodium intake, the SSI shows the actual sodium sensitivity independent of the magnitude of the change in sodium intake (2,10). We chose to use

Table 2—*Characteristics of 16 patients with normotension and their hemodynamics, plasma renin activity, and urinary albumin excretion during the study*

	Patients with normoalbuminuria and normotension		Patients with microalbuminuria and normotension	
	Low sodium intake	Ordinary sodium intake	Low sodium intake	Ordinary sodium intake
n	8		8	
Sex (M/F)	5/3		4/4	
Age (years)	59 ± 11		61 ± 10	
BMI (kg/m^2)	21.8 ± 2.4		23.5 ± 4.7	
Fasting plasma glucose (mmol/l)	6.63 ± 0.91		6.76 ± 0.85	
HbA_{1c} (%)	8.4 ± 1.1		8.4 ± 2.1	
Systolic blood pressure (mmHg)	114 ± 12	121 ± 14‡	125 ± 5	136 ± 9‡
Diastolic blood pressure (mmHg)	70 ± 5	70 ± 5	74 ± 3	80 ± 5†
Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})	108 ± 18	118 ± 16‡	104 ± 15	115 ± 19*
Renal plasma flow (ml · min^{-1} · 1.73 m^{-2})	—	599 ± 111	—	500 ± 127
Plasma renin activity (ng · ml^{-1} · h^{-1})	3.0 (0.9–4.3)	0.5 (0.2–0.8)§	0.8 (0.4–1.4)	0.3 (0.2–0.4)§
Urinary albumin excretion (mg/day)	10.3 (8.1–18.0)	9.9 (7.2–18.2)	36.6 (23.5–56.5)	48.6 (32.3–68.7)§

Data are *n*, means ± SD, or median (25th to 75th percentile). *P = 0.020; †P = 0.0021; ‡$P < 0.001$ vs. low sodium intake. P value by Wilcoxon's signed-rank test: §$P <$ 0.02 vs. low sodium intake.

diets with 80 mmol sodium/day for the low level and 200 mmol sodium/day for the ordinary level of intake. By the classic method, 10 mmol sodium/day for the low level and 250 mmol sodium/day for the ordinary level should be chosen, as mentioned earlier. However, these levels of sodium intake are somewhat extreme for actual use, especially the lower level. We used a more practical level—80 mmol sodium—for a low sodium level; this level is close to that recommended by the sixth report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (18), and we advised patients to aim for that level of intake after discharge. Another advantage of the method we adopted is that the SSI can be used to assess the sodium sensitivity of blood pressure without need for the definition of sodium-sensitive and -resistant groups.

When normal kidneys excrete sodium, the slope of the pressure-natriuresis curve is very steep (2,19,20); as a result, blood pressure is typically not sodium-sensitive. When the slope is less steep, the pressure-natriuresis relationship shows that a much higher blood pressure is needed if more sodium is to be excreted. This is considered sodium-sensitive blood pressure. There is a close relationship between sodium sensitivity and glomerular capillary hypertension (2,21), and glomerular capillary hydraulic pressure is elevated in all animal models examined in which the blood pressure is sensitive to changes in sodium intake (2). Thus, in sodium-sensitive states, whether the whole-kidney ultrafiltration coefficient is decreased or tubule sodium reabsorption is increased, the glomerular capillary hydraulic pressure is elevated to compensate for the impaired sodium excretion. Both sodium sensitivity and glomerular hypertension are adaptations that overcome the decreased ability of the kidneys to excrete sodium.

The results of our study in type 2 diabetic patients with albuminuria are consistent with the above description. In diabetic and normotensive patients with micro- or macroalbuminuria, the systemic blood pressure is sodium sensitive, unlike that of patients with normoalbuminuria. In addition, the glomerular capillary pressure is probably elevated, causing albuminuria. Recently, using a method for the estimation of glomerular capillary pressure in type 2 diabetic patients with albuminuria, we found increases in the glomerular pressure, which causes albuminuria, and decreases in the whole-kidney ultrafiltration coefficient compared with type 2 diabetic patients with normoalbuminuria (22). However, in diabetes, albuminuria is caused not only by glomerular hypertension but also by glomerular structural damage because of the metabolic abnormalities.

In one study of patients with essential hypertension and without diabetes, the sodium-sensitive patients had microalbuminuria, but the sodium-resistant patients did not (23). The mechanism of albuminuria in diabetic nephropathy may differ from that in essential hypertension. The sodium sensitivity of blood pressure related to albuminuria seems to appear before hypertension in diabetic patients with albuminuria.

There are many reports about the cause-and-effect relationship between sodium sensitivity of blood pressure and insulin resistance. We did not investigate insulin resistance, so we cannot contribute to the discussion.

Several studies have shown that sodium and water retention are important in the initiation and maintenance of systemic hypertension in microalbuminuria and diabetic nephropathy; the contribution of the renin-angiotensin-aldosterone system to such retention in diabetes is small (24–27). Our results are in agreement with these reports and reiterate the importance of controlling systemic blood pressure according to recent guidelines: for nonpregnant diabetic patients ≥18 years of age, blood pressure should be maintained at <130 mmHg systolic and <85 mmHg diastolic (15,18). In our diabetic but normotensive patients with microalbuminuria, albuminuria decreased with the decrease in systemic blood pressure to <130/85 mmHg when the sodium intake was decreased.

In summary, even when the systemic blood pressure is within the normal range, sodium sensitivity of blood pressure in type 2 diabetic patients with early

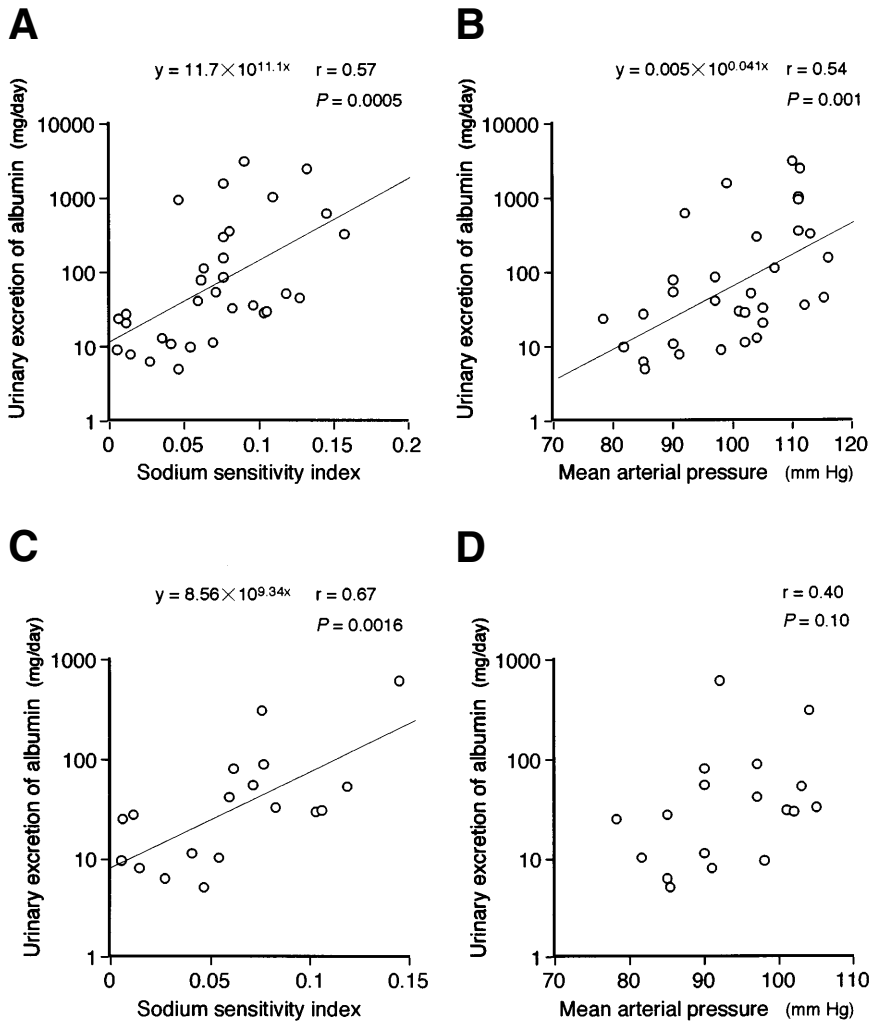

Figure 2—*Correlation of urinary albumin excretion with the SSI and that for all patients (*A *and* B*) and for the 18 patients with normotension (<140/90 mmHg) (*C *and* D*). Values for urinary albumin excretion and MAP were obtained when patients were on the diet with an ordinary salt level.*

nephropathy may be present, probably because of a decreased ability of the kidneys to excrete sodium. The correlation between SSI and albuminuria in diabetic patients with normal serum creatinine levels and with or without hypertension is consistent with glomerular hypertension being more important than systemic hypertension in the progress of nephropathy. In addition, our study showed that a low-sodium diet without medication can decrease systemic pressure from high normal to lower values in the reference range and can decrease the urinary excretion of albumin by diabetic patients with microalbuminuria.

Our study showed that in type 2 diabetic patients with albuminuria but normal serum creatinine levels, sodium sensitivity of blood pressure appears before hypertension and is related to albuminuria. Restriction of sodium intake is important for the treatment of the early nephropathy of diabetes, even when the patient is normotensive.

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