Intrarenal Hemodynamic Changes After Captopril Test in Patients With Type 2 Diabetes

A duplex Doppler sonography study

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OBJECTIVE — ACE inhibitors are known to be effective in preventing the progression of diabetic nephropathy. Activation of the renin-angiotensin system (RAS) is reported to contribute to intrarenal hemodynamic abnormality in diabetic patients. We examined whether RAS blockade by captopril induces intrarenal hemodynamic changes in normotensive patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — The patients ranged in age from 40 to 65 years (20 men and 20 women). A total of 15 age- and sex-matched healthy individuals served as control subjects. Resistive index (RI) of interlobar arteries was examined by duplex Doppler sonography before and after the oral captopril (25 mg) test.

RESULTS — At baseline, no significant differences in RI values or plasma renin activity (PRA) were seen between the patients and healthy subjects. In healthy subjects, the RI values after the captopril test were significantly higher than baseline values ($P < 0.01$). However, in patients with type 2 diabetes, both with normoalbuminuria and microalbuminuria, RI values after the test were significantly lower than baseline values ($P < 0.001$). There were significant negative correlations between ΔRI value and HbA_{1c} ($r = -0.458$, $P < 0.005$) and between ΔRI value and baseline PRA in diabetic patients ($r = -0.339$, $P < 0.05$). Multiple regression analysis showed that HbA_{1c} and baseline PRA significantly and independently affected the magnitude of decrease in RI values after captopril administration in diabetic patients ($R^2 = 0.391$, $P < 0.0001$).

CONCLUSIONS — These results indicate that the intrarenal RAS may be activated in diabetic patients, that such activation may be affected by poor glycemic control, and that blockade of RAS activation by ACE inhibitor reduces intrarenal vascular resistance in diabetic patients. The results emphasize the beneficial effects of ACE inhibition in improving intrarenal hemodynamics in diabetic patients.

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Abbreviations: EDV, end-diastolic flow velocity; PA, plasma aldosterone; PRA, plasma renin activity; PSV, peak systolic flow velocity; RAS, renin-angiotensin system; RI, resistive index; UAE, urinary albumin excretion.

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

Several studies ranging from pharmacology to genetics have indicated that the renin-angiotensin system (RAS) plays a role in the pathogenesis of diabetic nephropathy (1,2). Recently, hyperglycemia has been reported to induce intrarenal RAS activation in patients with type 1 diabetes (3). In type 2 diabetic patients with advanced nephropathy, intrarenal RAS activation is reported to be one of the mechanisms of renal hemodynamic changes and one of the important factors contributing to progression of diabetic nephropathy (4). In patients with both type 1 and type 2 diabetes, RAS inhibition by either ACE inhibitors or angiotensin receptor antagonists has emerged as a clear choice for prevention and treatment of diabetic nephropathy (5–7). Although a renoprotective effect of ACE inhibitors and angiotensin receptor antagonists has been demonstrated in diabetic nephropathy, little is known concerning the control of the renal circulation by RAS inhibition in diabetic patients.

Duplex Doppler sonography is useful for detecting intrarenal hemodynamic abnormalities such as those seen in obstructive renal diseases and renal allograft rejection (8,9). We previously demonstrated that resistive index (RI) measured by duplex Doppler sonography is useful for demonstrating hemodynamic abnormalities present in diabetic nephropathy (10,11). Interestingly, application of the captopril test to renal Doppler sonography is reported to be a noninvasive and inexpensive tool in screening studies aimed at diagnosing renovascular hypertension (12).

The objective of the present study was to examine whether blockade of RAS by the ACE inhibitor, captopril, has an effect on renal vascular resistance in patients with normotensive type 2 diabetes, including patients with early nephropathy, by duplex Doppler sonography. We evaluated the effect of captopril on intrarenal

Table 1—*Clinical characteristics of patients with type 2 diabetes and control subjects*

	Diabetic patients		Control subjects
	Group 2	Group 1	
Number	20	20	15
Sex (male/female)	10/10	10/10	8/7
Age (years)	51.8 ± 8.5	50.2 ± 7.8	48.4 ± 3.4
BMI (kg/m^2)	21.6 ± 3.4	22.8 ± 3.9	21.7 ± 3.7
Cigarette-years	216 ± 332	143 ± 250	197 ± 219
Duration of diabetes (years)	7.1 ± 6.1	5.2 ± 6.3	
Systolic blood pressure (mmHg)	121 ± 17	119 ± 15	119 ± 15
Diastolic blood pressure (mmHg)	71 ± 10	71 ± 12	69 ± 12
Fasting plasma glucose (mg/dl)	137 ± 41*	134 ± 29*	91 ± 6
HbA_{1c} (%)	8.8 ± 1.8	9.0 ± 1.6	
Creatinine (mg/dl)	0.65 ± 0.10	0.59 ± 0.14	0.66 ± 0.14
Total cholesterol (mg/dl)	194 ± 38	197 ± 29	181 ± 38
Triglycerides (mg/dl)	104 ± 33	88 ± 25	93 ± 36
HDL cholesterol (mg/dl)	56 ± 16	50 ± 12	57 ± 9
Diet alone/oral hypoglycemic agents/insulin	2/12/6	4/12/4	

Data are means ± SD. *$P < 0.01$ versus control subjects.

hemodynamic changes by examining changes in RI.

RESEARCH DESIGN AND METHODS

Subjects and clinical characteristics

A total of 40 normotensive Japanese patients with type 2 diabetes (aged 40–65 years) were enrolled. During the study period between May 1998 and April 1999, 232 diabetic patients without overt proteinuria were admitted to Osaka City University Hospital for treatment of diabetes or to attend a patient education course. Patients who met any of the exclusion criteria defined below were eliminated from the study, and the remaining patients who gave informed consent to participate in our study protocol were consecutively enrolled in the study. No patients were taking antihypertensive agents. The diagnosis of type 2 diabetes was established according to the Report of the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (13). Patients met three additional criteria for inclusion: no episodes of ketoacidosis, no ketonuria, and insulin therapy (if any) initiated after ≥5 years of known disease. After admission to our diabetes ward, medical examinations were performed to exclude other renal diseases. Patients with nondiabetic or obstructive kidney disease and those with microscopic or macroscopic hematuria, abnormal urinary sediment, history of glomerulonephritis or nephroureterolithiasis, dilated renal pelvis or atrophied kidney on ultrasonography, overt proteinuria, or elevated serum creatinine concentration (>1.2 mg/dl) were excluded. No patients had a clinical history or signs of cerebrovascular disease, peripheral vascular disease, or cardiovascular disease. During admission, each patient received a special diet (27–30 kcal/kg ideal body wt/day) that consisted of 50% carbohydrate, 30% fat, 20% protein, and 10 g salt per day. The study design was approved by the hospital committee on ethics. Each subject gave informed consent before entering the study. As a control, 15 age- and sex-matched subjects who visited our hospital for medical screening and gave informed consent were consecutively recruited from outpatient clinics of our hospital during the study periods. Inclusion criteria for nondiabetic control subjects were as follows: systolic blood pressure <130 mmHg and diastolic blood pressure <85 mmHg; fasting plasma glucose <126 mg/dl; no clinical history of myocardial infarction, cerebral infarction, or peripheral vascular disease; and no use of medication likely to affect renal or systemic hemodynamics.

For each diabetic patient, 24-h urine samples were collected on three consecutive days to determine the level of urinary albumin excretion (UAE) and creatinine clearance. In each patient, the level of 24-h UAE was the mean value for the 3 consecutive days. To examine the difference in responsiveness to captopril between the patients with normoalbuminuria and those with microalbuminuria, the patients were predefined as being in one of two groups: group 1, consisting of patients with UAE <30 mg/day ($n = 20$); and group 2, consisting of patients with UAE ≤30 or <300 mg/day ($n = 20$).

Blood pressure was recorded three times after a subject had rested in the supine position for at least 15 min. A standard mercury sphygmomanometer with a cuff that adapted to arm circumference was used. The systolic blood pressure was considered the point of first audibility of Korotkoff sounds, and the diastolic blood pressure was considered the point at which the Korotkoff sounds disappeared. The three measurements were averaged. In each patient, blood pressure was measured both before and 1 h after oral administration of 25 mg captopril.

Information on smoking habits was obtained by a self-administered questionnaire. Lifelong exposure to smoking was estimated as the product of years of smoking and the number of cigarettes smoked daily at the time of the study (cigarette-years).

Biochemical analysis

Blood samples were collected after an overnight fast for analysis of serum concentrations of creatinine, total cholesterol, triglycerides, and HDL cholesterol by standard laboratory methods. Plasma levels of glucose were measured by the glucose oxidase method, and HbA_{1c} was measured by high-performance liquid chromatography (HI-AUTO A1C; Sekisui Chemical, Osaka, Japan). The level of urinary albumin was measured in 24-h urine collections by immunoturbidmetry (TIA MicroAlb Kit; Nittobo, Tokyo, Japan). The UAE rate was expressed in milligrams per 24 h.

Blood samples for measuring plasma renin activity (PRA) and plasma aldosterone (PA) were collected after subjects had remained in the supine position for at least 15 min. PRA and PA were measured by radioimmunoassay (Dainabot, Tokyo, Japan). PRA and PA were measured both before and 1 h after oral administration of 25 mg captopril.

RI of interlobar arteries

To measure the RI, patients and healthy control subjects were asked to lie down

Table 2—*Changes in blood pressure, heart rate, PRA, PA, and RI from before to after the captopril test*

	Before the test	After the test
Systolic blood pressure (mmHg)		
Control	119 ± 15	109 ± 13*
Group 1	119 ± 15	107 ± 15*
Group 2	121 ± 17	109 ± 17*
Diastolic blood pressure (mmHg)		
Control	69 ± 12	65 ± 10†
Group 1	71 ± 12	65 ± 11*
Group 2	71 ± 10	66 ± 11*
Mean blood pressure (mmHg)		
Control	102 ± 13	94 ± 11*
Group 1	103 ± 13	93 ± 13*
Group 2	104 ± 14	95 ± 14*
Heart rate (bpm)		
Control	76 ± 11	73 ± 8
Group 1	75 ± 11	75 ± 11
Group 2	75 ± 11	75 ± 11
PRA (ng/ml/h)		
Control	1.837 ± 1.190	8.673 ± 8.390†
Group 1	1.594 ± 0.700	7.665 ± 8.879†
Group 2	2.064 ± 1.295	5.519 ± 8.616
PA (ng/dl)		
Control	11.993 ± 5.424	8.080 ± 4.001†
Group 1	14.941 ± 9.547	10.365 ± 3.761‡
Group 2	14.480 ± 6.776	10.864 ± 5.360‡
RI		
Control	0.662 ± 0.033	0.665 ± 0.032†
Group 1	0.676 ± 0.044	0.664 ± 0.045*
Group 2	0.679 ± 0.052	0.667 ± 0.050*

Data are means ± SD. *$P < 0.001$, †$P < 0.01$, and ‡$P < 0.05$ versus before the captopril test.

for at least 15 min before the examination. RI was measured as previously reported (10,11,14). In brief, the peak systolic flow velocity (PSV) and the end-diastolic flow velocity (EDV) were automatically calculated using the ultrasound apparatus. Flow velocities were determined from signals that were stable for at least five pulse beats, and measurements represented the average of five complete waveforms. The resistance parameter, RI, was determined as follows (10,11,14): RI = (PSV – EDV)/PSV.

Three different interlobar arteries from the right kidney were randomly selected and examined, and the mean value was calculated. The coefficient of variance for RI was 3.6%, as we reported previously (10,11).

The same procedure was followed 1 h after subjects were given 25 mg captopril orally. To avoid possible side effects, subjects were kept in the supine position and blood pressure was monitored every 30 min until the end of the study.

To evaluate the changes in RI after the captopril test, ΔRI was calculated by the following formula: (RI at 1 h after captopril administration) – (RI at baseline).

Statistical analysis

Values are expressed as mean ± SD. Values for clinical parameters were compared among three groups by one-way ANOVA with Scheffe's *F* test. Univariate χ^2 analysis was used for comparison by sex. The difference between values before and after captopril administration was examined by paired Student's *t* test. The relationships between ΔRI and biochemical variables were examined by linear regression analyses. A stepwise multiple regression analysis with forward elimination method was performed to evaluate the factors affecting ΔRI in patients with type 2 diabetes. The following independent variables were included in the model: age, BMI, duration of diabetes, smoking (cigarette-years), HbA_{1c}, total and HDL cholesterol, triglycerides, baseline mean blood pressure, and baseline PRA and PA as continuous variables; sex (female = 0, male = 1) was included as a categorical variable. The *F* value was set at 4.0 at each step. All statistical analyses were performed using Stat-View V software (Abacus Concepts, Berkley, CA) for a Macintosh computer. A level of $P < 0.05$ was accepted as statistically significant.

RESULTS

Clinical characteristics

The clinical characteristics of diabetic patients and control subjects are shown in Table 1. Diabetic patients were grouped by level of UAE. Among the three groups, no significant differences were found in sex, age, BMI, cigarette-years, systolic or diastolic blood pressure, creatinine, total cholesterol, triglycerides, or HDL cholesterol. Fasting plasma glucose was significantly higher in diabetic patients than in control subjects. There were no significant differences in the duration of diabetes, fasting plasma glucose, or HbA_{1c} between the two groups of diabetic patients.

Changes in blood pressure, heart rate, PRA, and PA after the captopril test

The changes in blood pressure, heart rate, PRA, and PA from before to after the captopril test are shown in Table 2. Systolic and diastolic blood pressures after the captopril test were significantly lower than before the test in both the control subjects and the two groups of diabetic patients ($P < 0.001$). In the control subjects, PRA after the captopril test was significantly higher than before the test ($P < 0.01$). In diabetic patients, PRA in group 1 was significantly higher after the captopril test than before it ($P < 0.01$), and in group 2 PRA was higher with borderline significance ($P = 0.06$). PA after the captopril test was significantly lower than that before the test in all three groups ($P < 0.01$ in control subjects; $P < 0.05$ in diabetic patients).

Changes in RI after the captopril test

No significant difference existed in baseline RI values among the three groups (Table 2), although RI values in diabetic patients tended to be higher than those in control subjects, as previously reported (10). In control subjects, the RI values after the test were significantly higher than

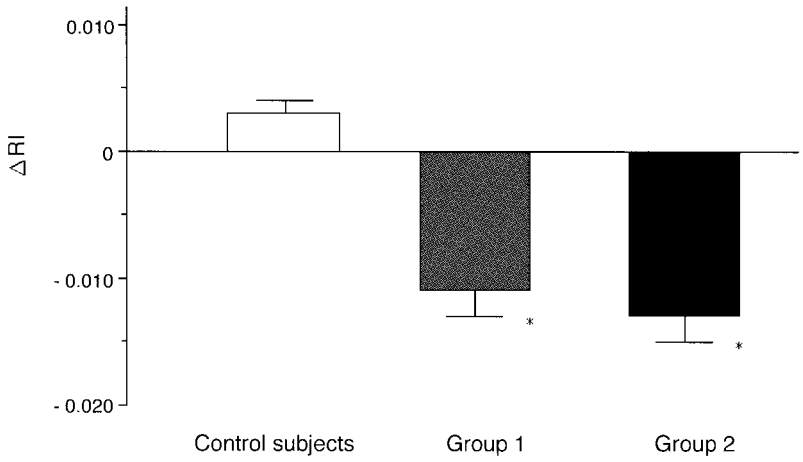

Figure 1—*Changes in RI (ΔRI) after captopril test in control subjects (□) and group 1 (▩) and group 2 (■) diabetic patients. There was a significant difference in ΔRI between control subjects and group 1 diabetic patients and between control subjects and group 2 diabetic patients. There was no significant difference in ΔRI between group 1 and group 2 diabetic patients.* * P < *0.0001 versus control subjects.*

those before the test ($P < 0.01$). RI values after the captopril test were significantly lower than those before the test in both groups with diabetes ($P < 0.001$), in contrast to the control subjects. There were no significant differences in RI values between the two groups of diabetic patients, either before or after the test (unpaired Student's *t* test).

Changes in RI value (ΔRI) are shown in Fig. 1. There were significant differences in ΔRI between the control subjects and group 1 of the diabetic patients ($P < 0.0001$) and between the control subjects and group 2 of the diabetic patients ($P < 0.0001$, unpaired Student's *t* test). There was no significant differences in ΔRI between the two groups of diabetic patients (unpaired Student's *t* test).

Correlation between ΔRI and clinical parameters in diabetic patients

Linear regression analyses were performed to examine the relationships between ΔRI and clinical parameters. Between ΔRI and HbA_{1c} in diabetic patients, there was a negative correlation with a coefficient of $r = -0.458$ ($P < 0.005$, Fig. 2). Between ΔRI and baseline PRA in patients, there was a negative correlation with a coefficient of $r = -0.339$ ($P < 0.05$). However, there was no significant correlation between ΔRI value and other clinical parameters in diabetic patients, including age, duration of diabetes, BMI , cigarette-years, blood pressure, total cholesterol, triglycerides, HDL cholesterol, and baseline PA. There was no significant correlation between ΔRI and changes in mean blood pressure, PRA, or PA in diabetic patients either.

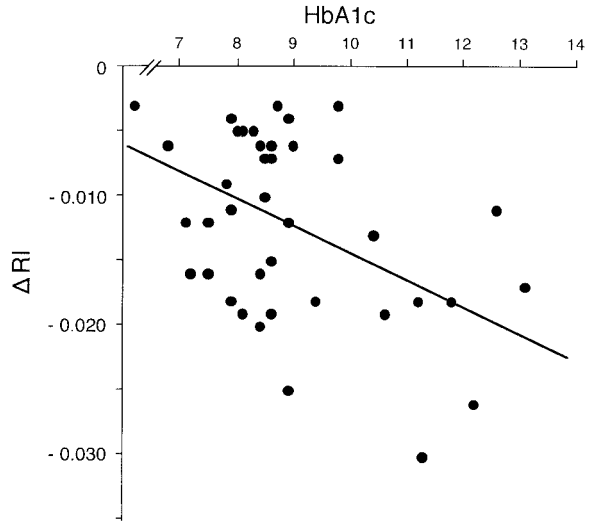

Figure 2—*Relationship between HbA_{1c} and change in RI (ΔRI). There was a significant negative correlation between HbA_{1c} and ΔRI* (r = *−0.458,* P < *0.005).*

Factors associated with ΔRI in diabetic patients

Results of a multiple regression analysis examining possible predictors independently affecting ΔRI in diabetic patients are shown in Table 3. HbA_{1c} and baseline PRA value significantly and independently affected ΔRI in diabetic patients ($R^2 = 0.391$, $P < 0.0001$)

CONCLUSIONS— In the present study, we examined intrarenal hemodynamic changes after the captopril test using duplex Doppler sonography to investigate the response to ACE inhibitors in patients with type 2 diabetes. We found a significant decrease in RI after the captopril test in patients with type 2 diabetes, in contrast to control subjects, in whom RI values were significantly increased. Poor control of blood glucose, as represented by increased HbA_{1c}, and basal PRA affected the magnitude of decrease in RI in patients with type 2 diabetes.

Veglio et al. (15) reported that in healthy subjects and patients with mild hypertension, RI values of interlobar arteries after the captopril (50 mg) test were significantly higher than those before the captopril test. In the present study, RI values in the control subjects were significantly increased after the captopril test, being consistent with the results of Veglio et al., despite the difference between studies in the dose of captopril used. A dose of 25 mg captopril was chosen for the present study, because of differences in body size between Caucasians and Japanese. Although the precise mechanism of increase in RI value is unknown, the increase in RI values in the control subjects could be related to functional vasoconstriction in the kidney (autoregulation), which may be induced by significant decrease in systemic blood pressure induced by captopril (15).

In contrast to the increase in RI values after the captopril test in control subjects, a significant decrease in RI after the cap-

Table 3—*Factors significantly affecting ΔRI in type 2 diabetic patients as determined by multiple regression analysis*

Variable			
Dependent	Independent	β	*F*
ΔRI	HbA_{1c}	−0.534	16.762
	basal PRA	−0.432	11.001
			$R = 0.391$ ($P < 0.0001$)

Significant predictors of ΔRI in patients with type 2 diabetes were explored among parameters including age, sex (female = 0, male = 1), duration of diabetes, BMI, cigarette-years, HbA_{1c}, baseline mean blood pressure, total cholesterol, triglyceride, HDL cholesterol, baseline PRA, and PA. The *F* value to enter was set at 4.0 at each step; β = standard regression coefficient; R^2 = multiple coefficient of variation.

topril test was seen in diabetic patients. Our results suggest the disruption of autoregulation in the kidney against decrease in blood pressure is present in diabetic patients. Although disruption of renal autoregulation was also reported in patients with advanced hypertension (15), our patients were all normotensive, suggesting that other mechanisms of decrease in RI values are present in diabetic patients. Because the average salt consumption by Japanese adults was 12.2–13.2 g/day during the 1990s, differences in salt intake between control subjects and diabetic patients (10 g/day) probably did not account for differences in RAS activity between control subjects and diabetic patients.

Examining 22 patients with renovascular hypertension, Veglio et al. (12) demonstrated that RI values after the captopril test were significantly decreased in kidneys with stenotic arteries but not in kidneys with nonstenotic arteries. This phenomenon is believed to be due to the dependency of the intrarenal vasculature on increased RAS activity in ischemic kidneys. In the present study, we found that one of the significant factors affecting the magnitude of decrease in RI value was baseline PRA. The higher the basal PRA was, the greater decrease in RI value after the captopril test was seen. These results suggest that diabetic kidneys may also depend on RAS activity, as seen in the ischemic kidneys of patients with renovascular hypertension. They also suggest that RAS activation may be present in the kidney of diabetic patients.

In fact, both experimental and clinical studies have shown that hyperglycemia induces RAS activation, leading to increase in renal vascular resistance. Woods et al. (16) demonstrated that intrarenal infusion of glucose in anesthetized dogs increased renin secretion. Using hyperglycemic clamp, Miller et al. (17) showed that, in patients with type 1 diabetes, hyperglycemia increased PRA and renal vascular resistance. Furthermore, recently, the angiotensin II type 1 receptor antagonist losartan was demonstrated to significantly increase renal plasma flow and significantly decrease renal vascular resistance in patients with type 1 diabetes, suggesting increased activity of the intrarenal RAS in diabetic patients (3). Price et al. (4) also found increased intrarenal RAS activity in type 2 diabetic patients with overt proteinuria, compared with healthy subjects, by demonstrating that a significant increase in renal plasma flow was induced by another angiotensin II type 1 receptor antagonist irbesartan. Mizuiri et al. (18) demonstrated increased immunostaining of angiotensin converting enzyme in the diabetic glomeruli, suggesting increased RAS activity in diabetic kidney. These reports, together with the present study, suggest that intrarenal hemodynamics change and become dependent on RAS activity in the presence of increased intrarenal RAS activity in diabetic patients. It has been reported that activation of RAS by hyperglycemia increases the renal vascular resistance in both type 1 and type 2 diabetes (3,17). In the present study, patients with relatively higher HbA_{1c} were included because they were treated for poor glycemic control, possibly leading to increased RAS activation. The decrease in RI values observed after the captopril test in the present study could be caused by elimination of intrarenal vasoconstriction after ACE inhibition. In the present study, the response to captopril (decrease in RI) was significantly affected by HbA_{1c} level. This result further indicates that intrarenal RAS activity is increased as glycemic control becomes poorer, consistent with the findings of the previous study (3,17). In the present study, there were no significant differences in response to captopril between patients with normoalbuminuria (group 1) and those with microalbuminuria (group 2).

The results of several studies, along with those of the present study, suggest that activation of the intrarenal RAS may be present in diabetic patients. The present study demonstrated that activation of intrarenal RAS could be caused by poor glycemic control and that blockade of RAS activation by ACE inhibition significantly reduced renal vascular resistance. By examining intrarenal hemodynamic changes, the present study has emphasized that relief from intrarenal RAS activation by strict control of blood glucose and/or use of RAS inhibition is important in improvement of renal hemodynamics and has provided evidence of a beneficial effect of ACE inhibition in diabetic patients.

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