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Intrarenal hemodynamic abnormalities in diabetic nephropathy measured by duplex Doppler sonography

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Intrarenal hemodynamic abnormalities in diabetic nephropathy measured by duplex Doppler sonography. Intrarenal hemodynamics were studied by duplex Doppler sonography in 112 inpatients with type II diabetes mellitus (DM; 65 males, 47 females, 58 ± 13 years old). The resistive index (RI) and pulsatility index (PI) of the interlobar arteries were calculated. The patients were divided into four groups: group I consisted of patients with urinary albumin excretion (UAE) < 20 μg/min ($N = 42$), group II with 20 ≦ UAE < 200 ($N = 28$), group III with UAE ≧ 200 ($N = 25$), and group IV with serum creatinine ≧ 1.5 mg/dl ($N = 17$). Both RI and PI values in groups II, III, and IV were significantly higher than those in the controls (age- and sex-matched healthy persons, $N = 37$; $P < 0.001$), and those in group IV were significantly higher than those in groups I, II, and III ($P < 0.0001$). Multiple regression analysis revealed that RI values in DM patients were significantly affected by creatinine clearance, age, and duration of diabetes ($R^2 = 0.554$, $P < 0.0001$). When intima-medial thickness (IMT) of the femoral and carotid arteries were measured by B-mode ultrasonography, RI values were significantly correlated with both the femoral and carotid arterial IMT. These results demonstrate that intrarenal hemodynamic abnormalities are present in type II DM patients with nephropathy, and that intrarenal hemodynamics are affected by decreased glomerular function and also probably by advanced arteriosclerosis.

Duplex Doppler sonography, which simultaneously measures both real-time and pulsed Doppler sonography, has been used clinically to examine intrarenal hemodynamic abnormalities such as obstructive renal diseases and renal allograft rejection [1–4]. In diseases limited to the glomeruli, such as glomerulonephritis, the clinical usefulness of this method is limited since the resistive index (RI), measured by pulsed Doppler sonography, is poorly correlated with serum creatinine levels [5]. In active tubulointerstitial diseases (acute tubular necrosis and tubulointerstitial nephritis) or vasculitis/vasculopathy, increased RI values have been reported [5]. The mechanisms leading to an increase in RI are not known. So far, few reports describing the application of duplex Doppler sonography in patients with diabetes mellitus (DM) have been published [6, 7].

In this report, we examined intrarenal hemodynamics in patients with type II DM and found intrarenal hemodynamic abnormalities in patients with nephropathy. We analyzed the factors associated with increased RI values. We further measured the intima-medial thickness (IMT) of the femoral and carotid arteries in these patients by high-resolution B-mode ultrasonography and compared the RI values and IMT of the two arteries. We found that increased RI values are significantly correlated with decreased glomerular function and probably with advanced arteriosclerotic lesions within the kidneys of these patients.

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Methods

Subjects

We evaluated 112 Japanese patients with type II DM. The diagnosis of DM was based on a previous history of diabetes or criteria according to the World Health Organization [8]. All patients were admitted to Osaka City University Hospital for the treatment of DM and an educational course on diabetes. As a control group, 37 age- and sex-matched subjects were examined. Each subject gave informed consent to participate in the study. None of the control subjects had proteinuria, renal insufficiency, diabetes, hypertension, cardiovascular disease, cerebrovascular disease, or peripheral vascular disease. In each diabetic patient, 24-hour urine collections were performed during three consecutive days in order to determine the level of urinary albumin excretion (UAE) and creatinine clearance. In each patient, the level of 24-hour urinary albumin excretion was the mean value from three consecutive days. Creatinine clearance was calculated from 24-hour urine samples and serum creatinine levels. Diabetic patients were divided into four groups according to UAE and serum creatinine levels as follows: group I consisted of patients with UAE less than 20 μg/min ($N = 42$); group II had a UAE equal to or more than 20 μg/min and less than 200 μg/min ($N = 28$); group III had a UAE equal to or more than 200 μg/min ($N = 25$); and group IV had a serum creatinine equal to or more than 1.5 mg/dl ($N = 17$). All the group IV patients had UAE of more than 200 μg/min. To exclude patients with nondiabetic or obstructive kidney diseases, the patients with microscopic or macroscopic hematuria, or an abnormal urinary sediment, a past history of glomerulonephritis or nephro-ureterolithiasis, or dilated renal pelvis on real-time ultrasonography, were excluded from this study. The patients who had severely atrophied kidney(s), either unilateral or bilateral, were also excluded from this study because

Table 1. Clinical characteristics of the control and diabetic subjects

	Control	Group I	Group II	Group III	Group IV
Number of patients *male/female*	37 (17/20)	42 (24/18)	28 (15/13)	25 (15/10)	17 (11/6)
Age *years*	58.5 ± 12.5	55.7 ± 14.0	61.7 ± 12.1	55.7 ± 11.6	64.7 ± 7.5
Duration of diabetes *years*	—	7.3 ± 5.7	13.2 ± 10.7	14.3 ± 7.2	17.1 ± 7.9
Body mass index kg/m^2	21.5 ± 1.8	22.5 ± 3.8	22.7 ± 3.3	22.6 ± 3.8	22.6 ± 3.8
Fasting plasma glucose *mg/dl*	81 ± 10	184 ± 64[b]	194 ± 81[b]	181 ± 56[b]	133 ± 46[a]
Hb A_{1C} %	—	10.2 ± 2.5	9.9 ± 2.6	9.3 ± 2.5	6.8 ± 1.5
Total cholesterol *mg/dl*	—	202 ± 45	211 ± 53	216 ± 63	242 ± 56
Serum creatinine *mg/dl*	0.69 ± 0.20	0.64 ± 0.20	0.63 ± 0.20	0.82 ± 0.39	3.44 ± 1.64[b]
Blood urea nitrogen *mg/dl*	14.9 ± 4.2	15.5 ± 4.2	18.0 ± 5.6	17.7 ± 6.1	43.8 ± 13.2[b]
Creatinine clearance *ml/min*	—	97.6 ± 37.9	91.2 ± 32.2	72.7 ± 29.9	14.4 ± 9.3
Mean blood pressure *mm Hg*	82 ± 13	91 ± 13	97 ± 13[a]	103 ± 17[b]	105 ± 8[b]

Data are expressed as the mean ± SD. HbA_{1C} is glycohemoglobin A_{1C}.
[a] $P < 0.01$ vs. control
[b] $P < 0.001$ vs. control

of poor imaging of blood flow with real time/color coded sonography and difficulty in detecting a waveform. Twenty-five diabetic patients were treated by diet alone (25 to 30 kcal per ideal body weight), 60 patients with sulfonylureas, and 27 with insulin therapy. As previously reported [9, 10], blood pressure was measured three times with a standard mercury sphygmomanometer and a cuff around the arm. Subjects rested in a supine position for at least 10 minutes before blood pressure measurements, and an average of the three measurements was documented. The clinical and biochemical characteristics of the control and diabetic subjects within each group are summarized in Table 1.

Biochemical analysis

Blood was drawn from patients in a supine position after an overnight fast for the analysis of plasma levels of glucose, hemoglobin A_{1C} (Hb A_{1C}), blood urea nitrogen, serum creatinine, and total cholesterol. Plasma levels of glucose were measured using the glucose oxidase method. Hb A_{1C} was measured by high-performance liquid chromatography (HI-AUTO A1C; Sekisui Chemical, Co. Ltd., Osaka, Japan). Blood urea nitrogen and serum and urine creatinine were measured by an autoanalyzer. Urinary albumin was measured in 24-hour urine collections by immunoturbidmetry (TIA MicroAlb Kit; Nittobo, Tokyo, Japan), and the UAE rate was expressed in $\mu g/min$.

Duplex Doppler sonography

Ultrasound examinations by a duplex Doppler apparatus were performed with subjects in a supine position after they rested for 15 minutes, as previously reported by us and others [2, 5, 6]. Images were obtained with a duplex Doppler apparatus (Aloka SSD 2000; Aloka, Tokyo, Japan) with a 5-MHz convex array probe in both real-time/color-coded Doppler and pulsed Doppler modes. The ultrasound probe was positioned gently on the flank in an oblique projection, and the kidney was visualized as a longitudinal image. To examine the interlobar arteries, we obtained real-time/color-coded Doppler mode images, in which intrarenal arterial and venous flows are shown in different colors. Sample volumes were obtained to position the cursor of the pulsed Doppler mode at the mid-portion of the interlobar arteries which flow along the renal pyramid. The pulsed Doppler mode was used to obtain quantitative measurements of velocity by placing a cursor along the course of the interlobar arteries. The sample volume was adjusted to a pulse length of 1.0 mm, and was estimated using the angle correction menu of the apparatus. The examination was completed in 15 minutes.

The peak systolic flow velocity (PSV), the end-diastolic flow velocity (EDV), and the time-averaged flow velocity (TAV) were automatically calculated by 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 parameters, resistive index (RI) and pulsatility index (PI), were determined as follows [1–3, 9, 11, 12]:

$$RI = (PSV - EDV)/PSV$$

$$PI = (PSV - EDV)/TAV$$

All measurements were performed by the same examiner (E.I.), who was unaware of the subject characteristics. Three different interlobar arteries from each kidney were randomly selected and examined, and a mean value from the two kidneys was calculated. When an RI or PI value deviated greatly from the other two values in a kidney, as sometime occurred in group IV patients, more than four RI and PI values from the kidney were obtained, the outlying values were omitted, and a mean of the remaining values was calculated. Since patients with unilateral atrophied kidneys were excluded from the study as stated above, significant differences in RI and PI values between the right and left kidney were not observed. Twenty-seven subjects (20 type II DM patients and 7 controls) were examined on two different occasions, separated by 2 to 10 days to estimate the intraobserver variability of the RI and PI values by the same examiner (E.I.), who was unaware of values from the first examination. The coefficient of variance for RI values was 3.8% and that for PI was 6.8%.

Measurements of intima-medial thickness of the carotid and femoral arteries

To measure intima-medial thickness (IMT), ultrasonographic scanning of the carotid and femoral arteries was performed with high resolution real-time ultrasonography using a 10-MHz in-line Sectascanner (SSD 650 CL; Aloka Co.), as described previously [10, 13–16]. Each subject was examined in a supine position. The carotid and femoral arteries were investigated bilaterally. The

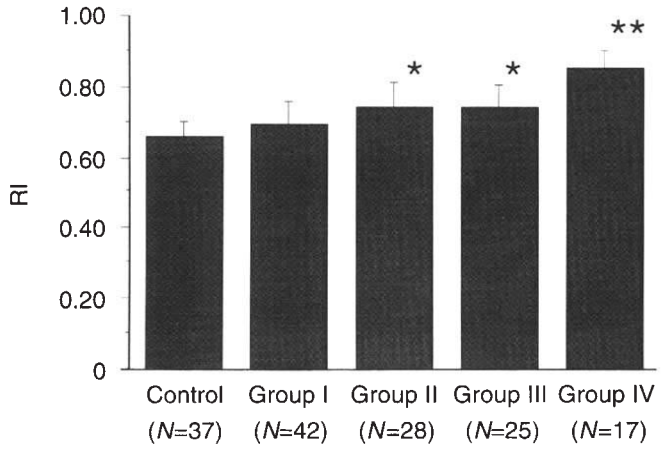

Fig. 1. *Resistive index (RI) of the interlobar artery of the control subjects and diabetic patients.* Group I consisted of patients with urinary albumin excretion (UAE) less than 20 μg/min ($N = 42$); group II had UAE ≧ 20 and < 200 μg/min ($N = 28$), group III had UAE ≧ 200 μg/min ($N = 25$), and group IV had a serum creatinine ≧ 1.5 mg/dl ($N = 17$). Data are expressed as the mean ± SD. *$P < 0.0001$ vs. controls; **$P < 0.0001$ vs. controls, group I, group II, and group III.

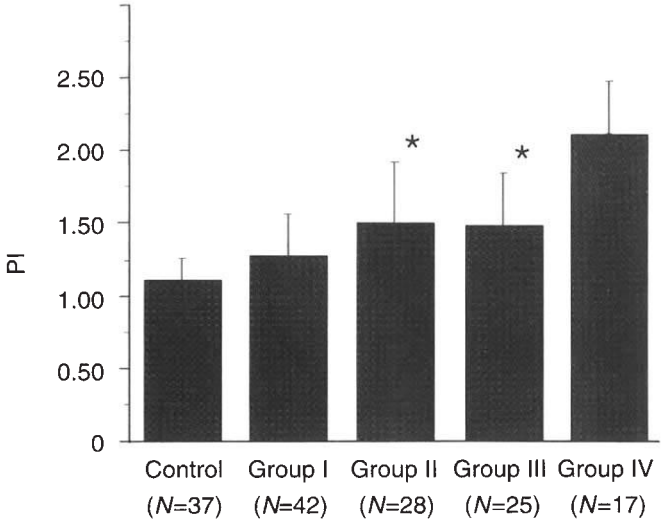

Fig. 2. *Pulsatility index (PI) of the interlobar artery of the control subjects and diabetic patients.* Group divisions are the same as in Figure 1. Data are expressed as the mean ± SD. *$P < 0.001$ vs. controls; **$P < 0.0001$ vs. controls, group I, group II, and group III.

carotid arteries were scanned at the levels of the bifurcation and the common carotid artery. The femoral artery was examined distal to the inguinal ligament at the site where the artery divided into the superficial and profundus femoral arteries. These regions were scanned bilaterally in longitudinal and transverse projections. The image was focused on the far wall of these arteries. The site of the most advanced atherosclerotic lesion and the projection that showed the greatest distance between the lumen-intimal interface and the media-adventitial interface [intima-media thickness (IMT)] was located in both the right and left carotid and femoral arteries [10, 13–15, 17]. IMT was measured from the digitized still images of the arteries during scanning. IMT was defined as the distance between the leading edge of the lumen-intimal interface to the leading edge of the media-adventitial interface of the far wall. Measurement of the far wall was chosen, since the luminal-intimal interfaces of the near wall were frequently invisible during our examinations (approximately 20% to 30% of examined cases) [10, 13, 16]. Three still images from the same section of the artery were measured, and a mean value was calculated.

Statistical analysis

Statistical analysis was performed with the Stat View IV system designed for the Macintosh Computer. All data are expressed as means ± SD. One-way analysis of variance (ANOVA, Scheffe's *F*-test) and chi-square test were performed for comparison of the control group and four subject groups. Multiple regression analysis was performed to assess the combined influence of clinical variables on the RI values. Correlation and linear regression analyses was performed to examine the relationship between RI values and creatinine clearance or age, and between the RI values and IMT of femoral or carotid arteries.

Results

RI and PI of intrarenal arteries in the control and diabetic subjects

RI values were 0.660 ± 0.041 in the control subjects, similar to previous reported value by us and others [1, 2, 4–7]. In the DM patients, RI values were 0.698 ± 0.058, 0.740 ± 0.074, 0.742 ± 0.066, and 0.852 ± 0.051 in groups I, II, III, and IV, respectively. RI values in the group I patients were higher than those in the control subjects, although this difference was not statistically significant ($P = 0.0965$). RI values in group II, III, and IV patients were significantly higher than those in the control subjects ($P < 0.0001$). Patients in the group with diabetic nephropathy with increased values of albuminuria and serum creatinine had increased RI values. The RI values in group IV were significantly higher than those in group I, II, and III patients ($P < 0.0001$), although statistical significance was not reached among the RI values in groups I, II, and III ($P = 0.0770$ between group I and II; $P = 0.0685$ between group I and III; not significant between group II and III; Fig. 1).

PI values were 1.107 ± 0.162 in the control subjects. In DM patients, PI values were 1.288 ± 0.270, 1.504 ± 0.428, 1.489 ± 0.368, and 2.111 ± 0.444 in groups I, II, III, and IV, respectively. PI values in group I patients were not significantly higher than those in control subjects ($P = 0.1665$). PI values in the group II, III, and IV patients were significantly higher than those in the control subjects ($P < 0.0002$, $P < 0.0006$, and $P < 0.0001$, respectively). Among the DM patients, PI values in group IV were significantly higher than those in groups I, II, and III ($P < 0.0001$, respectively), while there was no statistical significance among the PI values in group I, II, or III patients ($P > 0.1$; Fig. 2).

Since there were relatively larger standard deviations and coefficients of variance in PI values than in RI values, RI values were used in the following analysis to assess factors affecting intrarenal diabetic hemodynamics.

Analysis of clinical variables affecting RI values in diabetic patients

To examine the combined influence of clinical variables on RI values, a multiple regression analysis was performed with a model using creatinine clearance, age, duration of diabetes, fasting plasma glucose, Hb A_{1C}, total cholesterol, sex (male, 0; female, 1) and mean blood pressure as independent variables. Among these variables, RI values in DM patients were significantly affected by

Table 2. Clinical factors affecting the resistive index of the renal interlobar arteries

Variables				
Dependent	Independent	β	$P <$	R^2
Resistive index	Creatinine clearance	−0.364	0.0001	
	Age	0.277	0.0005	
	Duration of diabetes	0.221	0.0025	
	Fasting plasma glucose	−0.115	0.1951	
	HbA_{1C}	−0.119	0.2046	
	Total cholesterol	0.085	0.2410	
	Sex	−0.028	0.6966	
	Mean blood pressure	0.009	0.9071	0.554 ($P < 0.0001$)

Abbreviations are: β, standard regression; R^2, multiple coefficient of determination.

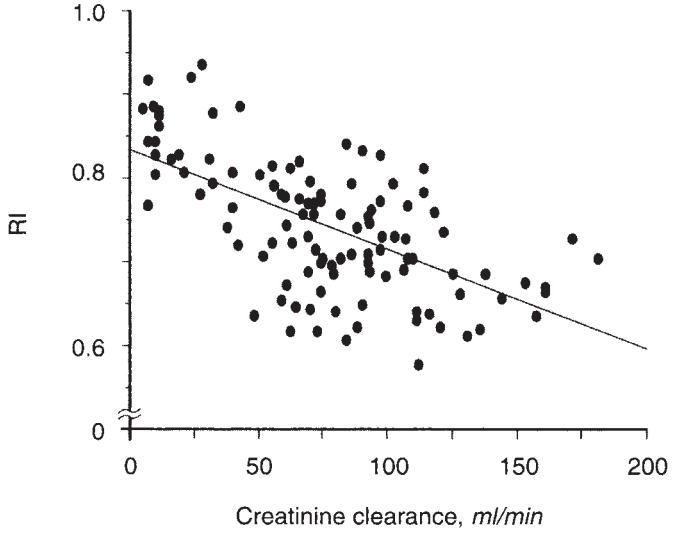

Fig. 3. *Correlation between the RI values and creatinine clearance in diabetic patients.* A significant, negative correlation existed between the two measurements. $r = -0.630$; $P < 0.001$.

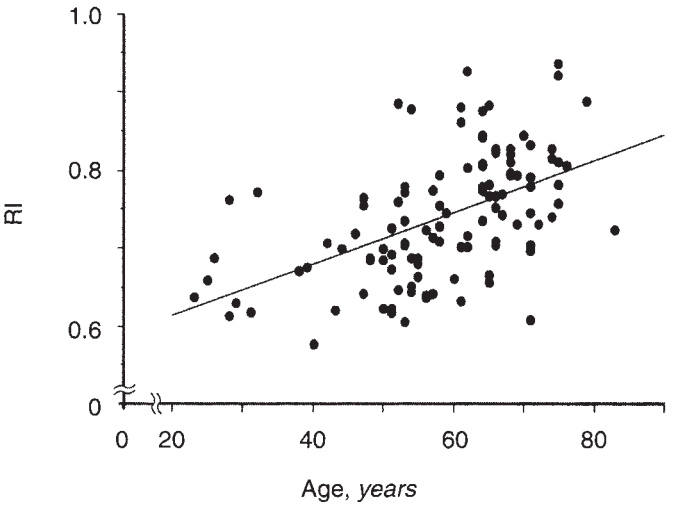

Fig. 4. *Correlation between the RI values and age of diabetic patients.* A significant, positive correlation existed between the two measurements. $r = 0.523$; $P < 0.001$.

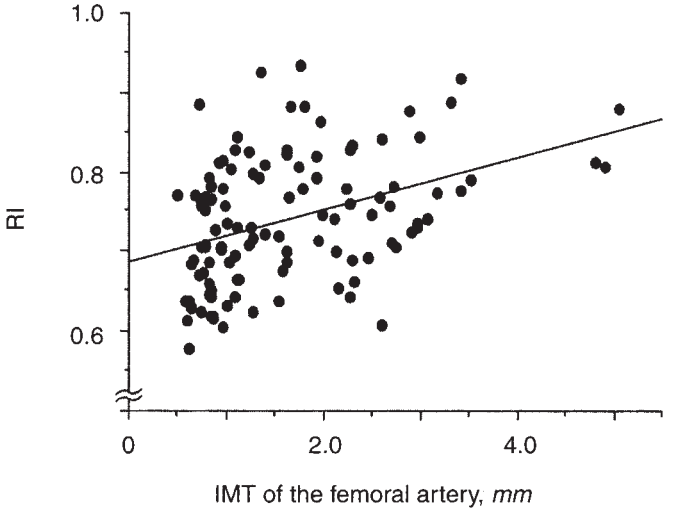

Fig. 5. *Correlation between the RI values and intima-medial thickness (IMT) of the femoral artery of diabetic patients.* A significant, positive correlation existed between the two measurements. $r = 0.391$; $P < 0.001$.

creatinine clearance ($\beta = -0.364$), age ($\beta = 0.277$), and duration of diabetes ($\beta = 0.221$; $R^2 = 0.554$, $P < 0.0001$), but not by the other variables (Table 2).

The relationship between the RI values and creatinine clearance in diabetic patients showed a negative correlation coefficient of $r = -0.630$ ($P < 0.001$; Fig. 3). The relationship between the RI values and age of diabetic patients showed a positive correlation coefficient of $r = 0.523$ ($P < 0.001$; Fig. 4). There was no relationship between creatinine clearance and age in diabetic patients (data not shown).

Relationship between RI values and IMT of femoral or carotid arteries

To examine the relationship between RI values and arteriosclerosis, RI values were compared with the femoral and carotid IMT. Significant, positive correlations between RI values and IMT of the femoral arteries, and between the RI values and IMT of the carotid arteries existed ($r = 0.391$, $P < 0.001$, and $r = 0.264$, $P < 0.004$, respectively; Figs. 5 and 6).

Discussion

The use of duplex Doppler sonography to examine various renal disorders such as renal allograft rejection [1, 3], obstructive kidney disease [2], renovascular hypertension [18], and parenchymal renal disease [5] have been reported. We used sonography to examine intrarenal hemodynamic changes noninvasively in patients with type II DM. We demonstrated the presence of intrarenal hemodynamic abnormalities in type II DM patients with nephropathy, defined by the presence of increased albuminuria and renal insufficiency. From the resistance parameters used in the present study, RI values had a relatively smaller coefficient of variance and standard deviation than PI values, as seen in our previous study [6, 9]. A smaller standard deviation for RI values compared with PI values was also seen in a duplex Doppler

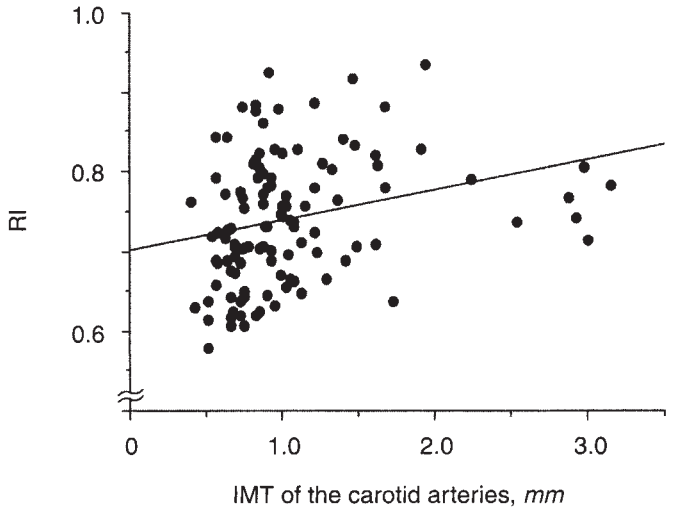

Fig. 6. *Correlation between the RI values and intima-medial thickness (IMT) of the carotid artery of diabetic patients.* A significant, positive correlation existed between the two measurements. $r = 0.264$; $P < 0.004$.

ultrasonography study of renal allografts [4]. Even using different resistance parameters, we found a significant increase in both RI and PI values in type II diabetic patients with nephropathy (groups II, III, and IV), compared to control subjects. These results partially agree with the results of a French study [7], in which RI values of DM patients both with and without renal insufficiency were shown to be significantly elevated. In that study, DM patients without renal insufficiency included both those with and without proteinuria. In our study, DM patients without renal insufficiency were further divided according to the levels of albuminuria. We found a significant increase in RI values in patients with UAE equal to or more than 20 μg/min (groups II and III), compared to age- and sex-matched control subjects. Further, a trend towards higher RI values was observed between patients in group II and group III and patients with a UAE less than 20 μg/min (group I).

In the present study, factors affecting the RI values were examined. In multiple regression analysis, the most significant factor affecting the RI values in DM patients was found to be creatinine clearance. As creatinine clearance decreased, RI values increased. This result is consistent with that of Platt et al [5], who demonstrated that in various renal diseases, RI values of patients with normal creatinine levels were significantly lower than those with elevated creatinine levels, despite a weak correlation between serum creatinine levels and RI values ($r = 0.34$). However, compared to their results, we found that the correlation coefficient between creatinine clearance and RI values was relatively high ($r = -0.630$). These results may be due to differences in the method used in assess renal function, as serum creatinine levels were measured in their study and creatinine clearance in our study. In addition, they may be attributable to differences in the disease populations, since their study included patients with a variety of diseases, such as glomerulonephritis, tubulointerstitial diseases and vasculitis/vasculopathy (the latter two had high RI values, seemingly independent of serum creatinine levels), and our study included type II DM patients only. Our results agree with those of Sauvain et al, in which DM patients with renal insufficiency showed higher levels of RI values than those without renal insufficiency [7]. Our present study clearly demonstrates that in patients with type II DM, creatinine clearance, which is closely related to glomerular function, is strongly and significantly correlated with RI values. The mechanisms for increased RI values in patients with decreased glomerular function is unknown. Sclerotic glomeruli in advanced diabetic nephropathy may cause increased blood flow resistance measurable at an upstream interlobar artery. In advanced diabetic nephropathy, glomeruli become sclerotic, tubuli become atrophic, and interstitial fibrosis is increased [19, 20]. Increased interstitial fibrosis may cause elevated RI values in advanced diabetic nephropathy, as elevated RI values have been reported in tubulointerstitial diseases [5].

By multiple regression analysis, the other significant factors affecting the RI values in DM patients were demonstrated to be age and duration of diabetes ($\beta = 0.277$ and $\beta = 0.221$, respectively). As age increased, RI values increased. Age was not significantly correlated with creatinine clearance, which had the greatest influence on RI values in the present study. There have been no previous reports demonstrating a relationship between increased RI values and age. Platt et al have reported that among patients with nonobstructive (medical) diseases, those with vasculitis/vasculopathy had extremely high RI values (mean RI = 0.82 ± 0.05) [5]. Frauchiger et al have recently reported that renal allografts with biopsy-proven vascular rejection showed greatly increased RI values (mean RI = 0.80 ± 0.18), although other types of rejection showed relatively normal RI values [1]. These results strongly suggest that intrarenal vasculopathy causes high RI values. In the present study, factors associated with intrarenal vasculopathy could be considered in diabetic patients. It is well known that advanced arteriosclerosis occurs with increasing age [13–15, 21–25]. In addition, diabetes is a strong risk factor for arteriosclerosis [15, 26–30], and a long duration of diabetes is a significant risk factor for advanced arteriosclerosis [14, 15, 31, 32]. Taken together, one can speculate that significant contributions of patient age and duration of diabetes to increased RI values may be due to advanced arteriosclerosis. Furthermore, renal diseases, defined as microalbuminuria and macroalbuminuria in DM patients, is known to be a risk factor for widespread vascular damage [28, 32]. Microalbuminuria has also been demonstrated to be a predictor of vascular disease in nondiabetic subjects [33–35]. These suggest that the significant increase in RI values in patients with microalbuminuria and macroalbuminuria (groups II and III) may have been caused by increased vascular damage (arteriosclerosis).

To further examine the possible contribution of advanced arteriosclerosis to increased RI values of the interlobar artery, we studied the relationship between RI values and the IMT of the femoral and carotid artery. We found significant, positive correlations between RI values and the femoral artery IMT, and between RI values and the carotid artery IMT. Although the sizes of the femoral and carotid artery are different from that of the interlobar artery of the kidney, the extent and severity of arteriosclerosis of the medium-sized arteries (such as the carotid and femoral arteries) and small-sized arteries (such as the coronary and renal arteries) have been reported to be correlated in autopsy studies [36, 37]. According to an extensive autopsy study performed in a well-defined population in a limited region of Malmae, Sweden (69.8% of all deaths were autopsied during 1961

to 1962), significant correlations were found in the degree of arteriosclerosis among the carotid, femoral, and renal arteries (including the orifice of segmental arteries; $P < 0.01$), and their correlation coefficients ranged from 0.28 to 0.38 [36]. A close association of arteriosclerosis among arteries of different size has been demonstrated [24, 25, 29–31, 36–39], showing the systemic nature of arteriosclerosis and its relationship to hypertension, age, and diabetes mellitus. However, arteriosclerosis varies to a certain extent among arteries of different size, as shown in the Malmae study [36]. Thus, the significant correlations between IMT of the two arteries and RI values of the interlobar artery are indirect evidence for the possible contribution of advanced intrarenal arteriosclerosis to increased RI values. Arteriosclerosis in the kidney frequently causes tubular atrophy and interstitial fibrosis. Advanced tubulointerstitial lesions may contribute to increased RI values in these patients, since tubulointerstitial lesions have been reported to result in elevated RI values [5]. We have previously reported that uremia accelerated arteriosclerosis of the carotid and femoral arteries [10]. Contribution of decreased creatinine clearance to the increased RI values may, in part, be via accelerated arteriosclerosis induced by uremia.

Histopathologically, nephropathy in type II diabetes is considered to be different from that in type I diabetes and to be more heterogeneous [40, 41]. Gambara et al evaluated pathologic changes in 52 type II diabetics with overt clinical nephropathy, and found two types of pathologic changes (Class I and Class II) in addition to glomerular lesions unrelated to diabetes (Class III) [40]. Class I (37%) changes are similar to those seen in the nephropathy of type I diabetics, with glomerular hypertrophy and typical diabetic glomerulosclerosis. Class II (30%) changes are nonspecific, frequently with global glomerulosclerosis, interstitial fibrosis, tubular atrophy, and severe arteriosclerosis. The latter type (Class II) of overt clinical nephropathy in type II diabetics was considered to consist of chronic vascular (arteriosclerotic type) and tubulointerstitial lesions. Actually, in most patients with diabetic nephropathy, both types are thought to occur together [42–44]. In the present study, even in the patients with similar values for creatinine clearance or urinary albumin excretion, differences in resistance parameters were present. Considering that arteriosclerotic lesions or interstitial lesions that are frequently associated with diabetic nephropathy may be associated with increased RI values, measurement of resistance parameters could provide a useful information about such lesions [40, 42–44]. Arteriosclerotic lesions and/or tubulointerstitial lesions cannot be identified by blood analysis or assessment of albuminuria [40]. They can only be identified by histologic examination of renal tissue specimens obtained invasively [40]. As Gambara et al could find no difference between the clinical outcomes of patients with Class I or II lesions because of a relatively short duration of observation [40], further prospective studies are needed to establish if patients with higher RI values but a similar degree of albuminuria and creatinine clearance progress more rapidly to end-stage renal failure. Recently, angiotensin converting enzyme (ACE) inhibitors have been shown to delay the progression of diabetic nephropathy, slowing the decrease in glomerular filtration rate by decreasing the intraglomerular capillary pressure [45–47]. Patients with extremely high RI values compared to those with lower ones who have a similar creatinine clearance and degree of albuminuria may be more susceptible to ACE inhibitor-induced renal ischemia, as are patients with atherosclerosis or renal artery stenosis [48, 49].

Among resistance parameters measured by duplex Doppler sonography, RI values have been most frequently used in clinical practice. Our study also demonstrated that RI values are more useful than PI values because of smaller coefficients of variance and standard deviations. In our previous study, the intra-operator coefficients of variance were small, less than 5% [6]. However, normal ranges for RI values varied among reports by other authors who used different sonography machines and examined subjects of different ages with different diseases. It is reported to vary from 0.58 to 0.68 in normal (control) kidneys or normally functioning allografts [1, 2, 4–7, 18, 50]. In our study, RI values in control subjects (0.660 ± 0.041) who were relatively older (58.5 ± 12.5 years) were a little higher than the previous report. Since a weak positive correlation existed between age and RI values in the control group (although not statistically significant) and the mean age of seven patients with RI values exceeding +1 SD was 68 years, the normal range of RI values may be affected by age. It also has been shown that heart rate can affect RI values [50], although it is almost negligible in practice [1]. Although it is difficult to set a normal range for RI because of limitations in the gold standard proof of normal renal status, particularly considering the possible influence of age-related arteriosclerosis on RI values, Platt suggested 0.70 as a reasonable upper limit for normal RI values after examining patients with various renal diseases [5]. In our study, mean RI values of patients with microalbuminuria, overt proteinuria, and renal insufficiency were all above the limit suggested by Platt. Thus, we consider that an RI values greater than 0.70 suggests advanced glomerular lesions and/or arteriosclerotic lesions in type II diabetics who average 60 years old, even though the normal RI values may vary among operators or sonography machines.

In conclusion, the present study demonstrates that duplex Doppler sonography is useful in the noninvasive assessment of intrarenal hemodynamic abnormalities present in diabetic nephropathy. In addition, RI values may be a more useful marker for the assessment of intrarenal hemodynamics than PI values. RI values were significantly affected by decreased glomerular function, advanced age, and long duration of diabetes. The latter two factors may affect RI values through advanced arteriosclerosis, and the association of arteriosclerosis was also suggested by significant correlations between RI values and IMT of the femoral and carotid artery. Although further studies are needed, RI values may be a useful tool to evaluate the arteriosclerotic lesions of intrarenal small arteries in patients without renal insufficiency, since there are few useful methods to assess small artery lesions other than biopsy or post-mortem examination.

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