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# Associations of renal vascular resistance with albuminuria and other macroangiopathy in type 2 diabetic patients

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*Objective*- Albuminuria can be caused by endothelial dysfunction as a result of ischemic nephropathy rather than classical diabetic nephropathy. We studied whether renal vascular resistance (RI) of the main renal arteries could be associated with albuminuria, and further assessed the relationship between RI and aorta stiffness measured by brachial-ankle pulse wave velocity (baPWV).

*Research design and methods*- We consecutively studied 150 patients with type 2 diabetes mellitus (DM) and the absence of clinically overt RAS. Renal function expressed as eGFR (estimated glomerular filtration rate) was calculated using the modified formula of Modification of Diet in Renal Disease (MDRD). The RI ((peak systolic velocity – end-diatolic velocity)/peak systolic velocity) was measured with duplex Doppler ultrasonography.

*Results*- When the presence of albuminuria (uAlb) was defined as urinary albumin-to-creatinine ratio (μg/mg･creatinine) greater than 30, mean RI ((left RI+right RI)/2) was significantly higher in uAlb, compared with that in patients without uAlb. RI had significant associations with age (r=0.398, P<0.0001), diastolic BP (DBP) (r=-0.398, P<0.0001), eGFR (r=-0.373, P<0.0001), and baPWV (r=0.223, P<0.05), respectively. Multivariate logistic regression analysis showed that increased RI when defined as RI>0.72 (median) was significantly associated with age (P<0.01, 95%CI 1.02-1.19), DBP (P<0.01, 95%CI 0.86-0.97), and uAlb (P<0.01, 95%CI 1.53-15.46), respectively. Moreover, RI was an independent risk factor for uAlb after adjustment of both diastolic blood pressure and eGFR.

*Conclusions*- Renal vascular resistance was associated with albuminuria and aorta stiffness. Increased RI may imply the presence of any type of underlying renal damage including ischemic nephropathy.

Duplex Doppler ultrasonography (US) has been used to assess intrarenal hemodynamics. Resistive index (RI) calculated from blood flow velocities in vessles reflects renovascular resistance, and is known to increase in various disorders (1-5). Moreover, vasoactive agents, such as angiotensin II or angiotensin-converting enzyme inhibitors (6) are known to affect RI. Regarding mechanisms by which RI of intrarenal arterioles increases, we previously reported that arterio-arteriolosclerosis rather than interstitial fibrosis could play an important role (7). In addition, we reported that there was a direct relationship between RI and arteriolosclerosis in damaged kidneys, and RI at renal biopsy may be useful as one of the prognostic markers for renal outcome (7).

According to the annual report of Japan Dialysis Treatment Society in 2006, the most frequent cause of end-stage renal disease is diabetes mellitus (DM)(8). Although diabetic nephropathy has been considered to be a microvascular complication, histopathological examination of renal biopsies showed not only typical diffuse or nodular lesions, but also arteriosclerotic glomerulosclerosis (9). It has been reported that RI in patients with renal dysfunction (CRF) secondary to type 2 DM were significantly increased compared to the patients with non-diabeteic CRF (10). Furthermore, regardless of the status of microalbuminuria (MA), which has been considered to be a risk factor for diabetic nephropathy and progression of renal insufficiency, glomerular filtration rate (GFR) has also been reported to be correlated with RI (11). Indeed, there are several reports showing a correlation between RI and renal function (7, 11, 12). It is therefore conceivable that nonalbuminuric renal insufficiency (13) could be related to other pathogenetic disorders such as ischemic nephropathy rather than "classical" diabetic nephropathy. In this regard, it should be borne in mind that macroangiopathy, not microangiopathy, is likely to affect GFR because systemic atherosclerotic vascular disease adversely affects renal blood perfusion, resulting in a decrease of GFR even if clinically overt renal artey stenosis (RAS) is not evident. Ishimura et al. have already reported that RI values are significantly correlated with both femoral and carotid arterial intima-media thickness (IMT) in type 2 DM patients with nephropathy and that intrarenal hemodynamics are affected by decreased GFR probably through advanced arteriosclerosis (12). Recently, Ohta et al. have reported that increased RI of the main renal arteries is significantly correlated with the severity of systemic atherosclerosis (14). Furthermore, the intrarenal vascular resistance differs depending on the underlying renal disease, and appears to increase to a greater extent in diabetic nephropathy (14). However, the relationship between RI and albuminuria remains unknown despite albuminuria is known to be a strong predictor of cardiovascular events (CVE) caused by endothelial dysfunction (15).

Therefore, we assessed the relationship between RI of the main renal arteries and albuminuria. Moreover, we studied the severity of other macroangiopathy evidenced by an increase in aorta stiffness measured by brachial-ankle pulse wave velocity (baPWV), carotid intima-media thickness (IMT), and ankle-brachial pressure index (ABI) in association with RI.

## RESEARCH DESIGN AND METHODS

We consecutively studied 150 patients with type 2 DM attending the diabetes clinics in our hospital between March 2005 and June 2006. The diagnosis of DM was based on a previous history of diabetes or fulfillment of WHO criteria (16). Patients with known renal arterial stenosis, or those with malignancy or systemic disorders were excluded. The study protocol was approved by the Research and Ethics Committee of the

Shonan Kamakura General Hospital, and informed consent was obtained.

Blood was drawn in the morning after an overnight fast of at least 12 hours. Urinary albumin concentration was measured by enzyme-linked immunosorbent assay using fresh spot urine, and expressed as mg creatinine of urine. Normoalbuminuria (NA) was defined as urinary albumin-to-creatinine ratio < 30μg/mg in two or more urine samples and no more than one value ≧ 30μg/mg. Microalbuminuria (MA) was defined as urinary albumin-to-creatinine ratio > 30-299 μg/mg. Macroalbuminuria (DN) was defined by albumin-to-creatinine ratio > 300μg/mg. The presence of albuminuria was defined (uAlb) as urinary albumin-to-creatinine ratio (μg/mg・Cr) greater than 30. Renal function expressed by eGFR (estimated glomerular filtration rate) was calculated using the modified formula of Modification of Diet in Renal Disease (MDRD)(17):

$$\text{eGFR(male)(ml/min/1.73m}^2\text{)} = 0.741 \times 175 \times \text{Age}^{-0.203} \times \text{Cr}^{-1.154}$$

(if female: eGFR(male)x0.742)

Comorbidity was recorded and ischemic heart disese (IHD) was defined as the presence or any history of myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), or coronary artery bypass graft surgery (CABG). Cerebrovascular disease (CVD) was defined as the presence or any history of cerebral or cellebellar infarction or bleeding, or subarachnoidal hemorrhage. Peripheral arterial disease (PAD) was defined as the presence or any history of bypass surgery or percutaneous peripheral intervention or limb ischemia as evidenced by symptoms of intermittent claudication, resting pain or gangrene.

**Duplex Doppler ultrasonography:** All measurements were made after an overnight fast in a supine position and during suspended respiration at the end of inspiration. 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 pulse Doppler modes. The ultrasound probe was positioned gently on the flank in oblique projection, and the kidney was visualized as a longitudinal image. Doppler beam was placed on the main tract of the renal arteries. RI was calculated by the built-in software as follows:

RI= (peak systolic velocity – end-diatolic velocity)/peak systolic velocity. The use of antihypertenive agents was not suspended before the resistive index measument. Although the patients were not specifically screened for the presence of undiagnosed renal artery stenosis (RAS), we nevertheless measured the size of the nephrogram and blood flow at the hilum of each kidney. None of the patients that were included in the study had an hilar acceleration time > 100 cm/s or had evidence of kidney atrophy less than 8 cm. The average of right RI and left RI with the difference between the two kidneys not <15% was used as a marker of renal artery resistance in each individual.

Measurements were performed by well-trained staff without knowing any informations concerning the patients. Regarding reproducibility of measurements, inter-observer and intra-observer variances were 4.0 and 5.1%, respectively (7).

**Aorta Stiffness expressed as baPWV, ankle-brachial presure index (ABI) and carotid intima-media thickness (IMT):** Aortic stiffness can be assessed non-invasively by measurement of brachial-ankle pulse wave velocity (baPWV) (18). Recently, a new and simple device to measure baPWV has been developed. The device measures brachial-ankle pulse wave velocity using an oscillometric method (19). In this study, the baPWV was automatically calculated with the use of a Colin Waveform Analyzer (form PWV/ABI; Colin, Co., Ltd., Komaki, Japan). The instrument records baPWV, blood pressure, electrocardiogram, heart sounds, and ABI, simultaneously. Validity, reproducibility and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement have been reported elsewhere (19). Ankle-brachial presure index (ABI) was estimated by ankle systolic blood pressure/brachial systolic blood pressure.

According to our previous report (20), both carotid arteries were examined using a 7.5 MHz linear array transducer with high-resolution B-mode ultrasonography (Aloka, Tokyo, Japan). The intima-media thickness (IMT) was defined as the distance between the leading edge of the lumen-intima echo of the near wall and the leading edge of the media-adventitia echo. The maximum IMT was recorded in right and left carotid arteries, respectively.

As well as RI, baPWV, IMT, and ABI were expressed as an average of right and left measurements, respectively.

***Statistical analysis:*** All the data are expressed as mean □SD. Differences between the two groups were analyzed by an unpaired Student's t test. One-way analysis of variance (ANOVA) was used for multiple comparisons more than three groups followed by Scheffe's test. Logistic multiple regression analysis was performed to determine more related variables for RI. Increased RI when defined as RI greater than 0.72 (median) was used for logistic regression analysis. The F value for a candidate's entrance or removal from the discriminate function test was set at 4.0. The level of statistical significance was defined as $P<0.05$. All the statistical analysis was performed with SAS/Windows (Statview ver. 5.0).

## RESULTS

Basic characteristics of total 150 patients are shown in Table 1. Mean age ±SD was 66.1±10.2 years, and HbA1c was 8.01 ±1.81 %. Serum creatinine, and eGFR was 0.94 ±0.43 mg/dl and 77.6±22.0 ml/min/1.73m$^2$, respectively. Systolic (SBP) and diastolic blood pressures (DBP) both were relatively well controlled; SBP 139±21 mmHg, and DBP 79±14 mmHg, respectively. Comorbidity and co-current use of drugs are also shown in Table 1. The median of urinary albumin excretion was 22.8μg/mg・Cr. The RI of all patients was 0.720±0.071. The baPWV, IMT, and ABI were 1894±519 cm/sec, 0.943±0.123 mm, and 1.11±0.12, respectively (Table1).

RI was significantly higher in DN (0.745±0.077), compared with that in patients with NA (0.707±0.067) ($P<0.01$) as shown in Fig.1. Univariate regression analysis showed that RI had significant associations with age ($r=0.398$, $P<0.0001$), diastolic BP (DBP) ($r=-0.398$, $P<0.0001$) (Fig.2), eGFR ($r=-0.373$, $P<0.0001$), and baPWV ($r=0.223$, $P<0.05$) (Fig.3) (Table 2), respectively. Urinary albumin excretion, as a continuous variable, was not correlated with RI. Multivariate logistic regression analysis showed that independent of eGFR, RI was significantly associated with age ($P<0.01$, 95%CI 1.02-1.18), DBP ($P<0.01$, 95%CI 0.86-0.97) and uAlb (when the presence of albuminuria was defined as urinary albumin-to-creatinine ratio>30μg/mg:uAlb)($P<0.01$, 95%CI 1.53-15.46) (Table 3), respectively. However, baPWV, IMT, and ABI as well as eGFR, were not identified as independent risk factors for increased RI. Also, when uAlb was considered as a dependent variable, RI ($P<0.05$) as well as diastolic blood pressure ($P<0.05$) and eGFR ($P<0.01$) remained significant as independent risk factors.

## DISCUSSIONS

In the present study we showed that renal vascular resistance was higher in patients with macroalbuminuria. After an adjustment of eGFR, RI remained significant and was an independent risk factor for the presence of albuminuria. Therefore, RI is an useful marker for the presence of any type of nephropathy found in type 2 DM. When we consider the stages of diabetic nephropathy, it is plausible that there is a stage in which albuminuria and GFR do not always correspond to each other. Recent results regarding the pathophysiology of renal disease in type 2 DM have challenged the concept that a decline in renal function in patients with DM is always accompanied by an increased albuminuria. MacIsaac et al. have suggested that renal insufficiency, without albuminuria, is common in type 2 DM (11).

Increased RI is known to be correlated with renal dysfunction or urinary albumin excretion in hypertensive patients under treatment with angiotensin converting enzyme inhibitor (6). We showed that RI was correlated with macroalbuminuria. Recently, Nosadini et al. (21) have shown that increased renal arterial resistance predicts the course of renal function in type 2 diabetes with microalbuminuria. The patients with RI greater than 0.8 showed a significant deterioration in GFR. However, albumin excretion rate was similar in both the patients with RI above or below 0.8 at baseline although overt proteinuria tended to develop more frequently in patients with RI > 0.8. Therefore, the present study may indicate that RI was significantly correlated with albuminuria except in normoalbuminuric paients. Considering the finding that RI was not correlated with proteinuria in patients with idiopathic chronic glomerulonephritis (7), the results of the present study may also suggest the difference in the pathophysiological significance of albuminuria between both groups, CGN and DM, respectively. In DM patients, polyvascular disease based on systemic atherosclerotic disorders could affect renal injury through long-term intrarenal ischemia. Indeed, increased urinary albumin excretion can be a marker of coexisting coronary artery disease in patients with peripheral arterial disease (22). Atherosclerosis affects different vascular systems resulting in polyvascular disease. Recently, the REACH study has revealed that coronary, cerebral and peripheral arterial diseases are superimposed on one another (23). In the patients with DM, endothelial cells of the renal or intrarenal artery would be more affected by atherosclerosis, in addition to glomeruli, than those in the patients with CGN. On the other hand, albuminuria in the patients with CGN, may be more likely derived from glomerular capillary damage alone without (or with less) damage to the main renal artery. This may be the reason why RI was not correlated with proteinuria in the patients with CGN.

Renal injury in DM patients includes various pathophysiological disorders. In this regard, we need to be aware of ischemic nephropathy resulting from diminished renal blood perfusion even if clinically overt renal artery stenosis is absent. Ischemic nephropathy originally refers to the reduction of GFR that is caused by hemodynamically significant renal artery obstruction (24). However, the major clinical questions confronting the nephrologist in considering the diagnosis of ischemic nephropathy include “Which clinical or laboratory features are most useful in its detection?” The finding that increased RI of renal arteries is significantly correlated with albuminuria would provide a clue to study the clinical prognosis of less severe but long-term ischemic nephropathy. Endothelial cells in glomerular capillary could be easily injured by mechanical stress including ischemia. It has been recently reported that in proteinuric subjects even without DM there is evidence of macrovascular endothelial dysfunction remote from the kidney and of low-grade inflammation that is associated with microvascular endothelial dysfunction (25).

In conclusion, increased RI may imply the presence of any type of underlying renal damages including ischemic nephropathy resulting in endothelial dysfunction in type 2 diabetes.

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Figure.1 RI was significantly higher in patients with macroalbuminuria (DN) (0.745 ±0.077), compared with that in patients with normoalbuminuria (NA)(0.707±0.067)(P<0.01). MA refers to microalbuminuria.

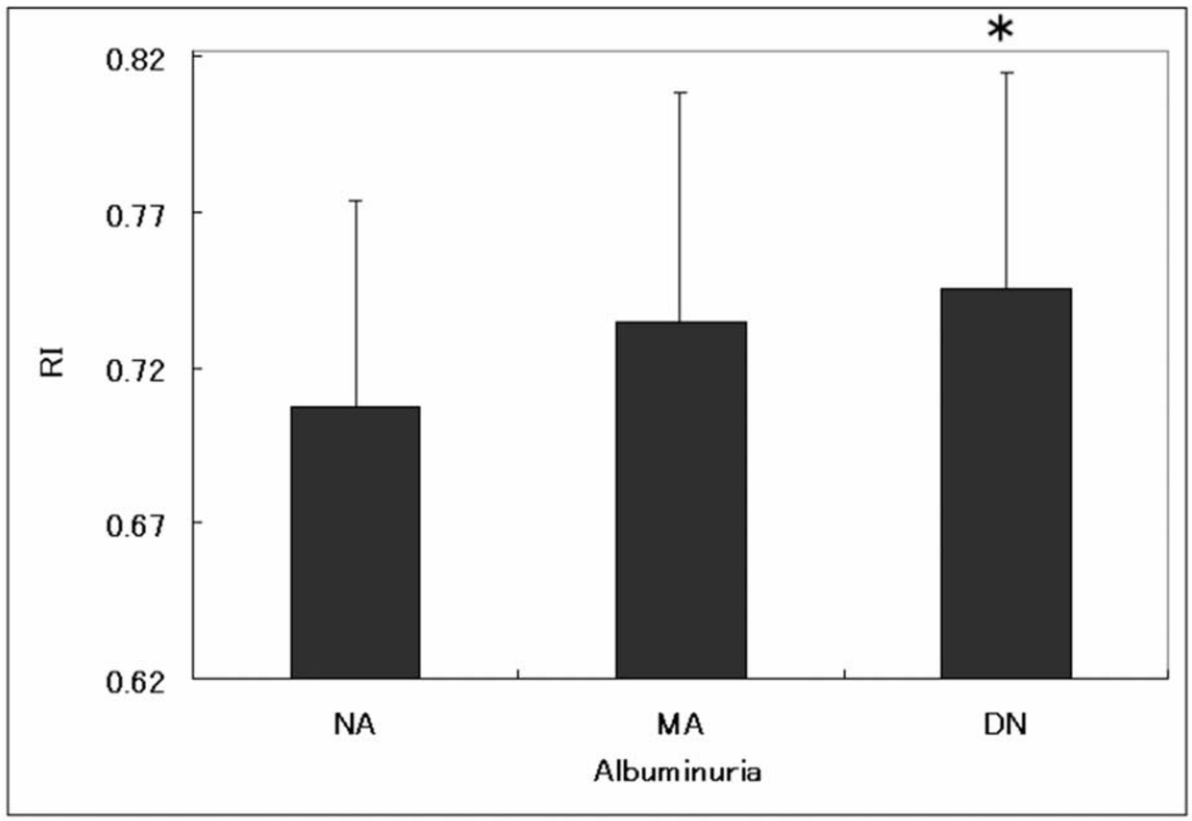

Table 1 Basic characteristics of the patients

| n=150 | Mean (SD) |
|---|---|
| Sex (M/F) | 102/48 |
| Age (years) | 66.1 (10.2) |
| HbA1C (%) | 8.01 (1.81) |
| SBP (mmHg) | 139 (21) |
| DBP (mmHg) | 79 (14) |
| TC (mg/dl) | 207 (40) |
| TG (mg/dl) | 170 (176) |
| HDL (mg/dl) | 54 (17) |
| Cr (mg/dl) | 0.94 (0.43) |
| eGFR (ml/min/1.73m$^2$) | 77.6 (22.0) |
| RI | 0.720 (0.006) |
| baPWV (cm/sec) | 1894 (510) |
| IMT (mm) | 0.94 (0.23) |
| UAE (μg/mg・creatinine) | 215.1 (640) |
| (Comorbidity) | |
| Hypertension (%) | 72.0 |
| Hyperlipidemia (%) | 64.0 |
| IHD (%) | 35.3 |
| CVD (%) | 8.7 |
| PAD (%) | 12.7 |
| (Drugs) | |
| ARB (%) | 50.7 |
| ACEI (%) | 14.0 |
| CCB (%) | 38.7 |

Abbreviations SBP;systolic blood pressure, DBP;diastolic blood pressure, TC;total cholesterol, TG;triglycerides, HDL;high density lipoprotein, Cr;creatinine, eGFR;estimated glomerular filtration rate, RI;resistive index, baPWV;brachial-ankle pulse wave velocity, IMT;intima-media thickness ABI;ankle-brachial pressure index, UAE;urinary albumin excretion, IHD;ischemic heart disease, CVD;cardiovascular disease, PAD;peripheral arterial disease, ARB;angiotension receptor blockade, ACE;angiotensin converting enzyme inhibitor, CCB;calcium channel blocker

Table 2. Univariate regression analysis associated with RI

| Variables | r | P |
|---|---|---|
| Age | 0.398 | <0.0001 |
| SBP | 0.136 | 0.126 |
| DBP | -0.398 | <0.0001 |
| HbA1C | 0.064 | 0.460 |
| UAE | 0.0616 | 0.882 |
| eGFR | -0.373 | <000.1 |
| baPWV | 0.223 | 0.015 |
| IMT | 0.142 | 0.154 |
| ABI | 0.167 | 0.065 |

Abbreviations: SBP; systolic blood pressure, DBP; diastolic blood pressure,
UAE; urinary albumin excretion, eGFR; estimated glomerular filtration rate,
baPWV; brachial-ankle pulse wave velocity, IMT; carotid intima-media thickness, ABI; ankle-brachial pressure index

Table 3. Multivariate logistic regression analysis associated with increased renal vascular resistance ($R^2$=0.246)

| Variables | β | Lower 95%CI | Upper95%CI | P |
|---|---|---|---|---|
| Age | 1.100 | 1.023 | 1.184 | 0.010 |
| SBP | 1.020 | 0.984 | 1.057 | 0.284 |
| DBP | 0.919 | 0.860 | 0.979 | 0.006 |
| HbA1C | 0.916 | 0.696 | 1.206 | 0.532 |
| uAlb | 4.862 | 1.529 | 15.45 | 0.007 |
| eGFR | 1.002 | 0.973 | 1.031 | 0.909 |
| baPWV | 0.999 | 0.989 | 1.000 | 0.169 |
| IMT | 2.179 | 0.229 | 20.72 | 0.497 |
| ABI | 20.77 | 0.242 | 1783.1 | 0.182 |

Abbreviations: SBP; systolic blood pressure, DBP; diastolic blood pressure,
uAlb; the presence of albuminuria over than 30μg/mg・creatinine, eGFR; estimated glomerular filtration rate,
baPWV; brachial-ankle pulse wave velocity, IMT; carotid intima-media thickness, ABI; ankle-brachial pressure index