Usefulness of the resistive index in renal Doppler ultrasonography as an indicator of vascular damage in patients with risks of atherosclerosis

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Abstract

Background. Chronic kidney disease (CKD) is caused by various risk factors of cardiovascular disease (CVD). The estimated glomerular filtration rate (eGFR) is commonly used for the evaluation of the renal function in patients with CKD; however, it is difficult to assess the pathogenesis of CKD and predict the renal prognosis accurately using only eGFR. The resistive index (RI) in renal Doppler ultrasonography (RDU) is thought to be a good indicator of renal vascular resistance caused by atherosclerosis. In the present study, we investigated whether RI could be used to evaluate the pathogenesis of renal damage and predict the renal prognosis and investigated the correlation between RI and blood pressure (BP) fluctuations in patients with or without hypertension.

Methods. The total study population included 194 patients (mean age: 66.2 years), who underwent RDU in our hospital ward between February 2009 and July 2010. We investigated the correlation between RI and multiple clinical parameters, including ambulatory blood pressure monitoring (ABPM).

Results. RI significantly correlated with age, eGFR, diastolic BP, pulse pressure and level of albuminuria. Patients with diabetes mellitus (DM) showed a significantly higher RI than patients without DM, although their eGFR was similar; thus, DM might accelerate renal vascular damage and RI could detect earlier changes of vascular damage preceding the time eGFR is reduced. Regarding ABPM, patients with a larger morning surge [systolic blood pressure (SBP) in the early morning—lowest SBP during sleep] showed a significantly higher RI.

Conclusions. The present study indicated that RI might be very useful for the evaluation of very early renal damage more effectively than eGFR and that diurnal BP change might be partly due to the progression of atherosclerotic change in the kidney evaluated by RI.

Keywords: chronic kidney disease; hypertension; renal Doppler ultrasonography; resistive index

Introduction

Chronic kidney disease (CKD) is recognized as a major health problem worldwide because the incidence and prevalence of CKD are very high, and current evidence suggests that it is associated with adverse outcomes of not only renal disease but also cardiovascular disease (CVD) and premature death [1–5]. CKD is defined and classified based on the urinary protein level and estimated glomerular filtration rate (eGFR) calculated from the serum creatinine level, age and sex [6]. CKD is caused by various risk factors of CVD such as diabetes mellitus (DM) hypertension, chronic glomerular nephritis and ageing. eGFR is thought to be useful for renal function screening; however, it is generally difficult to assess the pathogenesis of CKD and predict the renal prognosis accurately using only eGFR. Therefore, in order to manage CKD patients according to their individual pathogenesis and prevent aggravation of the renal function, we propose that a more useful index that can evaluate both the renal function and severity of atherosclerosis and reflect the prognosis of kidney and CVD than eGFR is necessary.

The resistive index [RI: (peak systolic velocity / C0 end diastolic velocity)/peak systolic velocity at segmental arteries in kidney] in renal Doppler ultrasonography (RDU) is thought to be a good indicator of renal vascular resistance caused by atherosclerosis [7–9]. Previous reports have shown that RI is associated with the renal prognosis [10–14]. Also, there are reports that diurnal blood pressure (BP) changes such as the morning surge are related to the incidence of CVD and CKD [15–19]. However, information is limited regarding the relationship between renal vascular resistance/vascular damage evaluated by RDU and the pathogenesis of CKD including diurnal BP changes.

In the present study, we investigated the possibility of employing RI as a useful indicator reflecting the pathogenesis of renal damage including BP fluctuations.

Materials and methods

Study subjects

We studied 206 patients with and without CKD who underwent RDU consecutively in our hospital ward between February 2009 and July
RI and vascular damage

2010. Eleven patients were excluded because they were diagnosed with renal artery stenosis or acute renal failure, and one patient was excluded due to being a renal transplant recipient. Therefore, a total of 194 patients were investigated in this study. Subjects underwent biochemical examination of the blood and urine testing. For 88 of the 194 patients, ambulatory blood pressure monitoring (ABPM) to evaluate diurnal BP change was performed. The clinical parameters considered regarding correlation with RI were as follows: height, weight, body mass index (BMI) eGFR, serum lipid profiles, fasting blood glucose (FBG), glycated hemoglobin (HbA1c) several biochemical parameters, level of proteinuria, systolic blood pressure (SBP) and diastolic blood pressure (DBP), diurnal BP changes measured by ABPM, smoking history and drug profile. The study protocol was approved by the Clinical Investigations Ethics committee of Osaka University. The study was performed in adherence with the principles of the Declaration of Helsinki and according to Good Clinical Practice standards.

Ultrasoundographic determination

RI was calculated as:

\[ \text{RI} = \frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{peak systolic velocity}}. \]

Patients were placed in a supine position, and the size of the left and right kidneys and the flow velocity in the aorta and renal arteries was evaluated to detect morphological abnormality or renal artery stenosis. RI was determined in three different segmental arteries of both kidneys and expressed as the mean of these values. Doppler examinations were all performed by the three operators (T.K., K.K. and M.O.) using a XARIO SSA-660A ultrasound machine (TOSHIBA) with a 2.5-MHz sector transducer.

Renal function

eGFR was calculated using the following equation: $\text{eGFR} (\text{mL/min/1.73 m}^2) = 194 \times \text{Crn}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$ (if female) [20].

Blood pressure measurements

Conventional BP was measured by trained observers with an electronic sphygmomanometer (HEM-705IT or HEM-711; OMRON). Ambulatory BP was evaluated using portable monitors (FM-200; Fukuda Denshi) at sphygmomanometer (HEM-705IT or HEM-711; OMRON). Ambulatory Blood pressure measurements/C0 awakening) nocturnal BP fall (%) was calculated as (daytime SBP/C0 [21].

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Patients with DM showed a significantly higher RI than those without DM, even in those with an equivalent eGFR (Figure 1E). Females showed a slightly, but significantly, higher RI than males. Patients with advanced CKD stage showed significant higher RI than patients with earlier CKD stage (Figure 2).

Univariate analysis showed that RI was significantly correlated with age (Figure 1A), BMI, pulse pressure (Figure 1B), HbA1c, FBG, blood urea nitrogen, uric acid and level of proteinuria (according to American Diabetes Association classification [23], the albumin/creatinine ratio in spot urine was used to classify proteinuria; no proteinuria: $<30$ mg/g Crn, microalbuminuria: $30–300$ mg/g Crn, clinical albuminuria: $>300$ mg/g Crn) and RI was negatively correlated with the height, eGFR (Figure 1C), DBP (Figure 1D), level of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and serum albumin (Table 2). On the other hand, the SBP was not significantly correlated with RI (Figure 1E). Females showed a slightly, but significantly, higher RI than males. Patients with advanced CKD stage showed significant higher RI than patients with earlier CKD stage (Figure 2).

Subjects using antihypertensive agents, renin–angiotensin–aldosterone system (RAAS) inhibitors (ARB, ACEI, AB) and statins showed a significantly higher RI, respectively, than subjects not using these agents (Patients without RAAS inhibitors: $0.67 \pm 0.08$ versus patients with RAAS inhibitors: $0.71 \pm 0.08$, $P < 0.01$. Patients without statins: $0.68 \pm 0.09$ versus patients with statins: $0.73 \pm 0.07$, $P < 0.01$).

There were no significant correlations between RI and a smoking history (current, past or nonsmoker) and the serum triglyceride level (Table 2). Stepwise multiple regression analysis showed that DBP, SBP, eGFR, BMI, HbA1c and age were independently associated with RI (Table 3).

<table>
<thead>
<tr>
<th>Table 1. Baseline clinical characteristic of all subjects*.</th>
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</thead>
<tbody>
<tr>
<td>Men/women</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
</tr>
<tr>
<td>RI</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
</tr>
<tr>
<td>Treated with antihypertensive agents</td>
</tr>
<tr>
<td>Treated with RAAS inhibitors</td>
</tr>
<tr>
<td>Treated with statins</td>
</tr>
<tr>
<td>Subjects with type II DM</td>
</tr>
</tbody>
</table>

*Values are expressed as the mean ± SD (range) or numbers.

RI and vascular damage

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There were no significant correlations between RI and a smoking history (current, past or nonsmoker) and the serum triglyceride level (Table 2). Stepwise multiple regression analysis showed that DBP, SBP, eGFR, BMI, HbA1c and age were independently associated with RI (Table 3).

Subjects with DM showed a significantly higher RI than those without DM (Figure 3). To further evaluate the influence of DM on RI, we categorized subjects into five clinical groups according to eGFR (Group I: eGFR ≥ 90; Group II: 60–90; Group III: 30–60; Group IV: 15–30 and Group V: <15) and compared RI with or without DM for each group. In Groups I, II and III, patients with DM showed a significantly higher RI than patients without DM, even in those with an equivalent eGFR (Figure 4). In Groups IV and V, however, there were no significant differences in RI between patients with or without DM (Figure 4).

ABPM was performed in 88 patients to evaluate diurnal BP changes. Their baseline characteristics are listed in Table 4. The mean age was 71.1 ± 10.5 years. Univariate
analysis showed that RI was significantly correlated with the average pulse pressure and average DBP but did not significantly correlate with the average SBP. Similar results were obtained concerning the daytime average pulse pressure, DBP and SBP or night-time average pulse pressure, DBP and SBP. Patients with a larger morning surge (upper quartile: >32.5 mmHg) showed a significantly higher RI (0.73 ± 0.06) than other patients (0.70 ± 0.08) (P < 0.05).

Fig. 1. A scatter plot and regression graph of the RI and some clinical parameters. (A) The correlation of the RI and age: correlation coefficient of 0.660 with P < 0.0001. (B) The correlation of the RI and pulse pressure: correlation coefficient of 0.379 with P < 0.0001. (C) The correlation of the RI and eGFR: correlation coefficient of −0.513 with P < 0.0001. (D) The correlation of the RI and DBP: correlation coefficient of −0.573 with P < 0.0001. (E) The correlation of the RI and SBP: correlation coefficient of −0.057 with P = 0.5273.
In four clinical groups classified according to the nocturnal SBP fall (extreme-dipper, dipper, nondipper and riser), there was no significant difference in RI (data not shown).

**Discussion**

It has been reported that RI in RDU can be a useful predictor of the progression of renal dysfunction [10–14], and RI can noninvasively provide useful diagnostic information for various renal diseases. It has been reported that a higher RI is associated with poor allograft survival after renal transplantation [24], and RI can be predicted to improve the renal function or BP reduction after angioplasty in patients with renal artery stenosis [25].

RI has also been reported to be significantly correlated with organ damage. Previous studies revealed that the measurement of RI in addition to low-grade albuminuria was useful for target organ damage screening in patients with resistant hypertension [7], and RI values were independently correlated with carotid intima media thickness in patients with never-treated essential hypertension [8] and metabolic syndrome [9]. These results suggest that renal vascular resistance indicated by RI can reflect the degree of systemic atherosclerosis and that RI can be a useful marker to detect and evaluate atherosclerotic diseases due to CVD risk factors such as hypertension, diabetes, dyslipidemia and metabolic syndrome.

In the present study, we found that patients with a lower eGFR showed a higher RI and that RI clearly demonstrated the renal function as well as in previous reports [10–14]. Furthermore, RI was significantly correlated with the pulse pressure and DBP. With ageing or atherosclerotic disease, the arterial wall is generally stiffening, and the elasticity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>R-value</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>+0.660</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height (m)</td>
<td>-0.370</td>
<td>0.2136</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-0.056</td>
<td>0.2136</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>+0.131</td>
<td>0.0440</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>-0.057</td>
<td>0.5273</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>-0.573</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>+0.379</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>+0.167</td>
<td>0.0202</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>+0.168</td>
<td>0.0279</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>-0.209</td>
<td>0.0028</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>-0.217</td>
<td>0.0025</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>+0.074</td>
<td>0.8720</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>+0.313</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>UA (mg/dL)</td>
<td>+0.219</td>
<td>0.0015</td>
</tr>
<tr>
<td>Serum albumin (mg/dL)</td>
<td>-0.321</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>-0.513</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albuminuria (mg/g Crn)</td>
<td>+0.194</td>
<td>0.0161</td>
</tr>
</tbody>
</table>

**Table 3.** Stepwise multiple regression analysis of variables associated with the RI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP (mmHg)</td>
<td>53.489</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>28.627</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>11.114</td>
<td>0.0012</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>9.110</td>
<td>0.0032</td>
</tr>
<tr>
<td>Age (years)</td>
<td>5.900</td>
<td>0.0169</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>2.799</td>
<td>0.0974</td>
</tr>
<tr>
<td>Serum albumin (mg/dL)</td>
<td>1.557</td>
<td>0.2150</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>1.260</td>
<td>0.2644</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>0.880</td>
<td>0.3506</td>
</tr>
<tr>
<td>Albuminuria (mg/g Crn)</td>
<td>0.509</td>
<td>0.4775</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>0.174</td>
<td>0.6779</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>0.108</td>
<td>0.7432</td>
</tr>
<tr>
<td>UA (mg/dL)</td>
<td>0.087</td>
<td>0.7681</td>
</tr>
</tbody>
</table>

*Stepwise multiple regression analysis was performed using the following variables: DBP, SBP, HbA1c, eGFR, age, BMI, serum albumin, low-density lipoprotein (LDL) cholesterol, total cholesterol, albuminuria, BUN, high-density lipoprotein (HDL) cholesterol and UA.*
Taking RAAS inhibitors showed a significantly higher RI [33–35]. In the present study, however, subjects with type II DM had been under medical treatment such as receiving antihypertensive agents at the time of examination. Four clinical groups classified according to the nocturnal SBP fall (extreme-dipper, dipper, nondipper and riser) might not have shown a significant RI difference for a similar reason.

Elevation of RI is thought to be related to the activated systemic or renal RAAS, and RAAS inhibitors have been reported to reduce RI in diabetic nephropathy and hypertensive nephrosclerosis patients and exhibit a renoprotective effect [33–35]. In the present study, however, subjects taking RAAS inhibitors showed a significantly higher RI than subjects not taking these agents. Similarly, subjects taking statins showed a significantly higher RI than those without statins. This reason may be that doctors had dispensed medication such as RAAS inhibitors or statins at the time of investigation for the treatment of hypertension and dyslipidemia or prevention of renal dysfunction and atherosclerosis. Therefore, there is the same situation that the level of cholesterol showed a slight and negative correlation with RI.

It was reported that RI was higher in patients with DM compared with control subjects [36–41]. Also, patients with diabetic nephropathy have been reported to show a higher RI than those with chronic glomerulonephritis and with nephrosclerosis [42]. Although the exact mechanism of how DM affects RI has not been clearly demonstrated, it is thought that arteriolosclerosis has a greater impact on RI than interstitial fibrosis [43]. Other studies reported that macroangiopathy resulted from systemic atherosclerotic change that affects the renal blood perfusion and reduces GFR [44, 45]. Insulin resistance has been reported to be associated with increased RI independent of other factors in newly diagnosed type 2 DM and hypertensive patients [46].

In previous studies, however, there was limited information on the association between RI and DM in an equivalent GFR setting. Recently, CKD stages according to eGFR has been widely used to classify renal insufficiency. So, we hypothesized that patients with DM have a higher RI than those without DM in each comparable renal function group corresponding approximately to CKD Stages I–V, evaluated possible associations between RI and DM in an equivalent GFR setting and showed that DM may accelerate vascular damage and RI can detect this change more sensitively than eGFR. Although eGFR is a convenient and useful measure to evaluate renal function, it is difficult to assess the pathogenesis of CKD and predict the renal prognosis accurately by only eGFR. Our study suggests that RI may provide useful information on the renal function and severity of atherosclerosis and reflect the prognosis of kidney and CVD.

Diurnal BP change has been reported to be correlated with CVD and mortality [15–17], and it has also been correlated with renal insufficiency and the excretion of albuminuria [18, 19]. RI has been reported to be increased in patients with mild-to-moderate obstructive sleep apnea and 24-h diastolic BP [47]. However, insufficient studies have reported a relationship between renal vascular resistance/vascular damage evaluated by RI using RDU and diurnal BP change. In the present study, we found that patients with a larger morning surge showed a significantly higher RI, although we did not evaluate the sleep apnea. These findings suggest that diurnal BP change may be a risk factor for the progression of atherosclerotic change in the kidney and that diurnal BP change could be considered as a therapeutic target for renal protection.

The present study has several limitations. First, our study sample was relatively small and, in particular, the reasons why SBP did not show a significant correlation with RI on univariate analysis is that most of our subjects had been under medical treatment such as receiving antihypertensive agents at the time of examination. Four clinical groups classified according to the nocturnal SBP fall (extreme-dipper, dipper, nondipper and riser) might not have shown a significant RI difference for a similar reason.

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The present study has several limitations. First, our study sample was relatively small and, in particular,
only a limited number of patients with severe renal dysfunction (corresponding to CKD Stages IV and V) were included. Third, because this study recruited inpatients admitted to the university hospital, most patients had already been under medical treatment for hypertension, dyslipidemia and diabetes at the time of investigation; therefore, several parameters such as the BP, lipid profile and HaA1c might have been influenced by medical treatment. Finally, our study subjects were hospitalized for various reasons, and meal contents (i.e. sodium chloride intake) were not uniform.

In conclusion, RI might be very useful for evaluating the pathogenesis of renal damage more effectively than eGFR and predicting the renal prognosis in patients with risk factors of CVD. We also found that diurnal BP change might be a risk factor for the progression of atherosclerotic change should be considered as a therapeutic target for renal protection. Thus, RI evaluated by RDU may be very useful for the management of patients with CKD.

Conflict of interest statement. None declared.

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