Original Article

Predictors of Undiagnosed Renal Artery Stenosis among Japanese Patients with Risk Factors of Atherosclerosis

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Atherosclerotic renal artery stenosis (ARAS) is a significant cause of end stage renal dysfunction (ESRD) among the elderly. Although early detection of ARAS and induction of adequate treatment could reduce the incidence of ESRD, there have been few reports about parameters predictive of ARAS among Japanese. In this study, we investigated the clinical indicators that predict ARAS among Japanese with risk factors of atherosclerosis (>40 years of age plus hypertension, dyslipidemia or diabetes mellitus). After eliminating the patients who had already been diagnosed with renal artery stenosis, 202 patients were enrolled. The renal arteries of all 202 patients were evaluated by magnetic resonance arteriography (MRA), and the stenoses with >50% reduction in diameter at the ostium of the renal artery were defined as ARAS. MRA detected ARAS in 42 patients (31 hemilateral and 11 bilateral). Between the patients with and without ARAS there was no significant difference in gender distribution, detection of abdominal vascular bruits or smoking habit. The prevalences of diabetic, hypertensive and cerebrovascular comorbidity were also not significantly different. The mean blood pressure, body mass index and total serum cholesterol values were similar between the two groups. However, age, pulse pressure, serum uric acid, serum creatinine, amount of urinary protein, and coronary artery comorbidity were significantly higher, while estimated creatinine clearance was significantly lower in the patients with ARAS than in those without ARAS. A high prevalence of hypertensive retinopathy was also noted among patients with ARAS. Multivariate analysis revealed that older age and renal impairment were independent predictors of ARAS in Japanese patients with atherosclerotic risk factors. (*Hypertens Res* 2005; 28: 237–242)

***Key Words*: renal artery stenosis, renal impairment, aging, creatinine clearance, coronary artery disease**

Introduction

In Western countries, atherosclerotic renal artery stenosis (ARAS), which causes poorly controllable hypertension (HT) and progressive renal dysfunction, has become the leading cause of end stage renal disease (ESRD) in the elderly (*1*, *2*), and is estimated to be the underlying disease in 10 to 40% of patients entering dialysis treatments (*3*, *4*). Because of its progressive nature in the absence of adequate treatment, early

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Table 1. Baseline Clinical Characteristics in Patients with and without ARAS

	Total	Without	With	*p* value
Number	202	160	42	
Men/women	107/95	84/76	23/19	
% of men	53.0	51.2	54.8	0.79
Age (years)	61.8±11.2	60.2±10.8	67.7±10.8	<0.001
AVB	28 (13.9%)	19 (11.9%)	9 (21.4%)	0.11
Smoking	80 (39.6%)	66 (41.3%)	14 (33.3%)	0.35
HT	179 (88.6%)	141 (88.1%)	38 (90.5%)	0.67
DM	91 (45.0%)	72 (45.0%)	19 (45.2%)	0.98
Dyslipidemia	85 (42.1%)	70 (43.8%)	15 (35.7%)	0.35
CAD	18 (8.9%)	10 (6.3%)	8 (19.0%)	0.010
CBD	18 (8.9%)	14 (8.8%)	4 (9.5%)	0.88
SBP (mmHg)	142.2±20.1	141.3±20.1	146.6±20.0	0.14
DBP (mmHg)	81.5±12.9	82.2±12.5	79.0±14.2	0.16
PP (mmHg)	60.9±16.6	59.2±14.9	67.5±20.7	0.003
MBP (mmHg)	101.5±13.6	101.5±13.8	101.2±13.1	0.88
BMI (kg/m^2)	24.0±3.9	24.2±3.9	23.1±3.4	0.089
UA (mg/dl)	6.20±1.82	6.07±1.76	6.69±1.95	0.049
T Chol (mg/dl)	211.8±61.1	211.6±62.7	212.0±55.4	0.92
sCr (mg/dl)	1.42±1.29	1.24±1.02	2.10±1.87	<0.001
CCr (ml/min)	68.4±39.6	74.1±39.2	47.0±34.1	<0.001
u-Pro (g/gCr)	1.50±2.42	1.31±2.42	2.21±2.34	0.031

Data are presented as the mean±SD. ARAS, atherosclerotic renal artery stenosis; AVB, abdominal vascular bruits; HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CBD, cerebrovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MBP, mean blood pressure; BMI, body mass index; UA, serum uric acid concentration; T Chol, total cholesterol concentration; sCr, serum creatinine concentration; CCr, creatinine clearance; u-Pro, urinary protein.

detection of ARAS is mandatory to reduce the rate of dialysis induction (*2*). However, because antihypertensive agents that block the renin-angiotensin-aldosterone cascade have made blood pressure control possible even in patients with ARAS, patients with ARAS are often asymptomatic and many cases of ARAS are not detected until ESRD (*3*, *5*). Therefore, appropriate clinical indicators to detect ARAS at its early stage are required.

To detect ARAS, selective renal arteriography is the gold standard, but it is a too invasive method for screening. Computed tomographic arteriography (CTA) and magnetic resonance arteriography (MRA) are less invasive anatomical methods to evaluate the renal arteries. Owing to recent improvement in resolution, both CTA and MRA can detect most of the stenotic lesions in the main renal artery (*1*, *6*). However, considering the relatively higher incidence of contrast medium-induced nephro-toxicity, less invasive methods are appropriate for screening (*7*). Although Doppler ultrasonography is a non-invasive diagnostic method to detect vascular stenotic lesions, its sensitivity depends on the technique of the performer (*1*). A number of studies have already been conducted to estimate the predictors of ARAS in various populations using different methods (*1*, *6*, *8*). Long term HT, diabetes mellitus (DM), coronary artery disease (CAD), dyslipidemia, renal dysfunction and aging have been identified as concomitant risk factors. However, most of these studies were conducted in Caucasian populations, and there have been few reports on the factors predictive of ARAS in Japanese populations (*9*–*12*).

To elucidate the predicting indicators of ARAS among Japanese, we conducted a screening of ARAS in Japanese patients older than 40 years of age who were referred to our hospital and who had risk factors of atherosclerosis. ARAS was evaluated by MRA, and several clinical and biochemical parameters were compared between the patients with and without ARAS.

Methods

Patients

This study was carried out on 202 patients referred to the Division of Nephrology, Hypertension and Endocrinology, Tohoku University Hospital between January 2000 and December 2002. Patients were selected according to the following criteria: age >40 years with at least one of the risk factors of atherosclerosis (HT, dyslipidemia or DM). Patients with known stenotic lesions in the renal arteries and/or previously diagnosed with aortitis syndrome were excluded. The clinical and biochemical parameters shown in Table 1 were

Table 2. Hypertensive Retinopathy in Patients with and without ARAS

KWB grade	Total	Without	With
0	11 (11.2%)	11 (13.8%)	0 (0%)
I	32 (33.7%)	29 (36.3%)	3 (16.7%)
II	40 (40.8%)	31 (38.8%)	9 (50.0%)
III	13 (13.3%)	8 (10.0%)	5 (27.7%)
IV	2 (2.0%)	1 (1.3%)	1 (5.6%)

ARAS, atherosclerotic renal artery stenosis; KWB grade, Keith, Wagener and Barker grade.

measured in all patients. The renal arteries of patients were evaluated using contrast enhanced MRA. Informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of Tohoku University Hospital.

Laboratory Measurements and Definition

Serum creatinine (sCr), uric acids (UA), total cholesterol concentrations (T Chol) and urinary creatinine (uCr) were measured enzymatically. The amount of urinary protein (u-Pro) was measured in spot urine sampling and corrected by uCr (g/gCr). All blood and urine samples were obtained in a fasting state in the morning. Estimated creatinine clearance (CCr) was calculated according to the Cockcroft-Gault equation: CCr = (140 – age) × {body weight (BW) in kg} / {72 × (sCr in mg/dl)} (× 0.85 for female) (*13*). Body mass index (BMI) was calculated as (BW in kg) / (body height in m)^2. HT was defined as systolic blood pressure (SBP) >140 mmHg, diastolic blood pressure (DBP) >90 mmHg, or current use of antihypertensive medications. Pulse pressure (PP) was calculated as PP=SBP – DBP. Dyslipidemia was defined as pretreatment fasting T Chol >220 mg/dl or when patients had a history of dyslipidemia and were taking lipid-lowering medications. CAD and cerebrovascular disease (CBD) were considered to be present in patients whose vascular disease was previously confirmed by cardiac catheterization and computed tomographical analysis, respectively. Patients were considered to have DM if dietary and pharmacological interventions were required to maintain normal blood glucose levels.

Evaluation of the Main Renal Artery

MRA was performed with a 1.5 T magnet (Magneton Vision; Siemens, Erlangen, Germany). In all cases a Flash 3D T1-weighted sequence (TE/TR=4.6/1.8, Section thickness=1.5 mm, FOV=400, matrix=512 × 265) was used. Images were obtained by administering 0.2 ml/kg of Gd-DTPA with a power injector at a flow rate of 2 ml/s. Images were reconstructed using a standard maximum intensity projection algorithm and were reviewed by two radiologists who were blinded to the clinical data. A more than 50% reduction in the diameter of the main renal artery at the ostium in the two-dimensional (2D) plane was defined as ARAS. A decrease of 50% or more in the lumen diameter in 2D could be considered as a more than 75% decrease in the cross-sectional area of the lumen, which is thought to cause a clinically significant reduction in blood flow.

Fundal Examination

The fundal examination was carried out by midriatic retinography. Retinal changes were examined by a single ophthalmologist unaware of the patient's clinical characteristics. Hypertensive retinopathy was assessed according to the Keith, Wagener and Barker (KWB) classification and graded as follows: grade I, arteriolar diameter less than 50% of venous diameter; grade II, arteriovenous crossing changes situated at more than one papillary diameter from the papilla; grade III, presence of retinal hemorrhages or exudates; grade IV, presence of papillary edema accompanied by retinal hemorrhages or exudates.

Statistical Analysis

Discrete variables were expressed as counts and compared by χ^2 test. Continuous variables were shown as the mean±SD and compared by an unpaired *t*-test. To identify independent predictors for ARAS, we performed logistic regression analysis. Age, concomitant CAD, PP, UA, sCr, and u-Pro were entered into the model. All statistical analyses were performed using the SPSS software package (SPSS, Chicago, USA). Probability values of $p<0.05$ were considered to be statistically significant.

Results

The baseline clinical characteristics of enrolled patients are shown in Table 1. A total of 202 patients was enrolled. Among the 202 patients examined by MRA, 42 patients (20.8%) were found to have ARAS. The patients with ARAS (ARAS group) were significantly older than those without ARAS (non-ARAS group) (67.7±10.8 *vs.* 60.2±10.8 year-old; $p<0.001$), but there was no significant difference in gender distribution between the groups. The incidence of audible abdominal vascular bruits was higher in ARAS group than in non-ARAS group, but the difference was not statistically significant. The incidence of smoking, DM and dyslipidemia was also not significantly different between the groups. CAD comorbidity was more frequent in ARAS group (19.0%) than in non-ARAS group (6.3%) ($p=0.010$), but the incidence of CBD comorbidity was not different between the groups.

The prevalence of patients with HT and the value of controlled mean blood pressure (MBP) were not different between the groups, but ARAS group showed higher SBP and lower DBP. Accordingly, PP was significantly higher in

ARAS group than in non-ARAS group (67.5±20.7 *vs.* 59.2±14.9 mmHg; $p=0.003$). BMI and controlled T Chol were not significantly different between the groups. However, ARAS group had higher UA (6.69±1.95 *vs.* 6.07±1.76 mg/dl; $p=0.049$) and more severe renal impairment than non-ARAS group. ARAS group showed higher sCr (2.10±1.87 *vs.* 1.24±1.02 mg/dl; $p<0.001$), lower CCr (47.0±34.1 *vs.* 74.1±39.2 ml/min; $p<0.001$) and higher u-Pro (2.21±2.34 g/gCr *vs.* 1.31±2.42 g/gCr; $p=0.031$).

Of the 202 patients enrolled, fundal examination was performed in 98 patients (Table 2). Hypertensive retinal changes were evaluated according to KWB classification. Among the 98 patients examined, 18 patients (18.4%) were found to have ARAS. A high prevalence of hypertensive retinopathy was noted among patients with ARAS. Taking a retinal change of grade III or IV as severe hypertensive retinopathy, the incidence of accompanying severe retinopathy was significantly higher in patients with ARAS ($p=0.019$).

Multivariate analysis identified increasing age and impaired renal function as significant independent predictors of ARAS. The odds ratios for ARAS were 1.060 (95% confidence interval [CI], 1.024–1.098) of increasing age (/year of age) and 1.477 (95% CI, 1.149–1.899) of sCr (/mg/dl). The association of CAD and UA tended to have a higher odds ratio than these parameters, but the interaction did not reach the level of statistical significance.

Of the 42 patients with ARAS, 11 (26%) had bilateral ARAS. Table 3 summarizes the results of each parameter that showed a statistically significant difference between the ARAS and non-ARAS groups for both the hemilateral and bilateral ARAS subgroups. Although UA was slightly (but not significantly) lower in the patients with bilateral than in those with hemilateral ARAS, other indicators showed a more marked difference between these two groups. Patients with bilateral ARAS were older than those with hemilateral ARAS (73.2±6.2 *vs.* 65.7±11.5 years of age; $p=0.049$). PP was higher in bilateral than hemilateral ARAS patients (84.5±26.1 *vs.* 61.5±14.7 mmHg; $p<0.001$). Renal impairment was more severe in bilateral than hemilateral ARAS patients, as indicated by lower CCr, higher u-Pro and higher sCr. However, among the parameters of renal impairment, only the value of CCr showed a statistically significant difference between the groups (26.1±15.6 ml/min *vs.* 54.5±36.0 ml/min; $p=0.016$). CAD comorbidity was also more frequent among patients with bilateral ARAS (27.2% *vs.* 16.1%), although the number of patients was not sufficient to determine the statistical significance of this finding.

Table 3. ARAS Predictors between Patients with Hemi- and Bilateral Stenosis

	Total	Hemilateral	Bilateral	*p* value
Number	42	31	11	
Age (years)	67.7±10.8	65.7±11.5	73.2±6.2	0.049
CAD	8 (19.0%)	5 (16.1%)	3 (27.2%)	0.420
PP (mmHg)	67.5±20.7	61.5±14.7	84.5±26.1	<0.001
UA (mg/dl)	6.69±1.95	6.73±1.95	6.57±2.06	0.819
sCr (mg/dl)	2.10±1.87	1.88±1.73	2.75±2.19	0.186
CCr (ml/min)	47.0±34.1	54.5±36.0	26.1±15.6	0.016
u-Pro (g/gCr)	2.21±2.34	1.90±2.35	3.10±2.19	0.145

Data are presented as mean±SD. ARAS, atherosclerotic renal artery stenosis; CAD, coronary artery disease; PP, pluse pressure; UA, serum uric acid concentration; sCr, serum creatinine concentration; CCr, creatinine clearance; u-Pro, urinary protein.

Discussion

In the present study, the combined prevalence of hemilateral and bilateral ARAS was 20.8% in 202 randomly selected patients with atherosclerotic risk factors. Although this value does not reflect the prevalence of ARAS in the general elderly population of Japanese, our results indicate that ARAS is a relatively common entity among Japanese patients with atherosclerotic risk factors, just as it is in their Caucasian counterparts (*14*, *15*).

Atherosclerosis is a systemic disease, and atherosclerotic change occurs even in renal arteries without apparent stenotic lesions. Although such change does not manifest as ARAS in its early stages, it is thought to progress without apparent clinical symptoms and to develop into ARAS in its later stages (*2*). Therefore, it is anticipated that patients with more severe ARAS, which often occurs as bilateral ARAS, will tend to be older. In the present study, ARAS group was significantly older than non-ARAS group, and the patients with bilateral ARAS were older than those with hemilateral ARAS. These results support the notion that atherosclerotic vascular disease progresses in the absence of proper treatment, and thus that ARAS should be detected in its early stage.

Among the parameters we evaluated, the prevalence of CAD comorbidity was significantly higher in ARAS group than non-ARAS group. This prevalence was similar to that reported for the Caucasian population, in which the prevalence of ARAS has also been reported to be high in patients with CAD (*15*). A high prevalence of ARAS in patients with CAD was also reported in a cohort of Asians that included Japanese (*5*, *10*, *11*). Because these studies reported a correlation between CAD severity and concomitant ARAS, ARAS should be detected and adequately treated to reduce the mortality rate in patients with CAD (*16*). Appropriate treatments that reduce the activity of the renin angiotensin aldosterone system would improve the prognosis of patients with CAD and ARAS (*17*–*19*).

Among the parameters of blood pressure, PP was significantly higher in ARAS than in non-ARAS group ($p=0.003$). Because PP has been reported to be a risk factor of atherosclerosis independent of MBP, the higher PP might have contributed to the progression of ARAS (*20*, *21*). However, the multivariate analysis did not identify PP as an independent predictor of ARAS. The sub-analysis of correlations among

the parameters entered into the multivariate analysis revealed a significant correlation between PP and age ($p<0.01$). Therefore, the contribution of PP to predict ARAS became negligible after the entrance of age as an explanatory variable for ARAS. Age was more significant as a predictor of ARAS than PP.

Other atherosclerotic risk factors (smoking habit, HT, DM and dyslipidemia) did not show a significantly different prevalence between ARAS and non-ARAS groups. In the Caucasian population, several studies have similarly reported the lack of any apparent correlation, while others have shown a correlation between these risk factors and ARAS (*14*, *15*, *22*, *23*). The discrepancy among these studies may reflect differences in the study design. In the present study, the prevalence of HT and DM was much higher than that in the general Japanese population. The high percentage of hypertensive and diabetic patients enrolled in the present study might conceal the correlation of HT and DM with ARAS.

Renal function was impaired more severely in ARAS group than in non-ARAS group in the present study, as was also reported in several studies conducted in Caucasian-based populations (*1*, *2*, *22*). In bilateral ARAS patients, more advanced renal dysfunction was also noted. Because renal function is known to decrease with age, the finding that renal function was more impaired in ARAS group might be considered to reflect an age-related reduction in renal function. However, multivariate analysis revealed that renal impairment was related to ARAS independent of aging in the present study, and impaired renal function could be considered an independent predictor of ARAS.

It has been reported that sCr does not correctly reflect renal function (*13*). Even in cases of moderate renal dysfunction, sCr does not increase if the muscle volume of the patients is reduced. Estimating renal function by CCr is a useful method in these cases (*13*). In the present study, both sCr and CCr were significantly different between ARAS and non-ARAS groups, but CCr showed a more significant difference than sCr ($p=6.7\times10^{-5}$ *vs.* $p=8.5\times10^{-5}$). CCr was also the only parameter that showed a significant difference between hemi- and bilateral ARAS. Because the value of CCr is calculated from—and thus dependent on—that of sCr, we did not include CCr in the multivariate analysis, but CCr could be used as a more accurate predictor of ARAS than sCr.

A higher value of UA was noted in ARAS group than non-ARAS group. However, because the value of UA is affected by renal function, this difference might reflect the fact that renal function was more impaired in ARAS group than in non-ARAS group. In support of this notion, UA was eliminated as an explanatory variable for ARAS from the model of multivariate analysis. The reported reduction of UA after surgical improvement of renal perfusion in the patients with renovascular hypertension also supports this notion (*24*).

Severe hypertensive retinopathy was detected at a significantly higher rate in ARAS than in non-ARAS group. A high comorbidity of ARAS with hypertensive retinopathy has also been detected in Caucasian patients with hypertensive retinopathy of KWB grade III or IV (*25*). In the present study, elevation of sCr, which would reflect the hypertensive renal impairment, but not SBP, DBP or PP, was revealed to be an independent predictor of ARAS. Therefore, comorbidity of ARAS with hypertensive retinopathy is considered to indicate a correlation of ARAS with hypertensive vascular damage but not high blood pressure, *per se*.

In summary, ARAS was found to be a relatively common disorder in elderly Japanese patients with atherosclerotic risk factors, just as previously reported for their Caucasian counterparts. Aging and renal impairment were identified as independent predictors of ARAS. Although CAD was not an independent predictor of ARAS, more severe ARAS was detected among the patients with CAD indicates these patients should be screened for early detection of ARAS. Using the predictors revealed in the present study, ARAS could be detected and treated appropriately in its early stages, which would decrease the mortality rate and the prevalence of ESRD among elderly Japanese.

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