Nephrol Dial Transplant (2011) 26: 3943–3949
doi: 10.1093/ndt/gfr141
Advance Access publication 28 March 2011

Associations of renal vascular resistance with albuminuria in adolescents and young adults

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Abstract

Background. Renal vascular resistance [resistive index (RI)] has been associated with albuminuria in patients with type 2 diabetes. We studied the correlations between renal artery RI and urinary albumin excretion in adolescents and young adults.

Methods. From May 2006 through September 2008, we established a cohort of adolescents and young adults based on previous history of elevated blood pressure (EBP) or normal blood pressure in childhood. This cohort was selected from the 1992–2000 nationwide mass urine screening of school children aged 6–18 years in Taiwan. From October through December 2008, we called back these adolescents and young adults living in Taipei to participate in a renal vascular stiffness study. Linear mixed regression models were applied to study the correlation

between renal artery RI and urinary albumin excretion after controlling for cardiovascular (CV) risk factors.

Results. Of the 147 subjects enrolled in this study, 67 had macroalbuminuria, 36 had microalbuminuria and 44 had normoalbuminuria. Except for high-density lipoprotein cholesterol, most CV risk factors did not differ significantly among these three groups. Mean RI were similar for the three groups. Neither log (urinary albumin concentration) nor log (urinary albumin:creatinine ratio) correlated with RI. Step-wise linear mixed regression models showed that RI was significantly associated only with male gender and diastolic blood pressure, but not with urinary albumin excretion or EBP in childhood.

Conclusion. Renal artery RI is not associated with urinary albumin excretion in nondiabetic adolescents and young adults.

Keywords: albuminuria; aortic stiffness; microalbuminuria; resistive index

Introduction

Microalbuminuria is not only a predictor of diabetic nephropathy [1], but epidemiologic and experimental data have shown that microalbuminuria is also associated with an increased risk for all-cause mortality, cardiovascular (CV) mortality, cerebrovascular disease (CVD) and, possibly, peripheral arterial disease [2, 3]. Albuminuria has been associated with CV morbidity and mortality in both diabetic and nondiabetic adults. These correlations between microalbuminuria and CVD have been demonstrated in diabetic patients, in nondiabetic hypertensive adult patients and in the general population [4–8]. Moreover, this correlation is observed even at levels of albuminuria below the conventional threshold for microalbuminuria [9, 10]. In addition, microalbuminuria has been associated with novel markers of subclinical atherosclerosis, such as increasing carotid artery intima-media thickness (IMT) and left ventricular hypertrophy [11]. Thus, microalbuminuria has been proposed as an integrated marker of subclinical organ damage in patients with primary hypertension [11, 12]. However, the role of elevated albumin excretion as an early marker of CV risk in adolescents and young adults has not yet been studied.

Vascular Doppler ultrasonography has been used to assess intrarenal hemodynamics in clinical nephrology. The most widely used parameter in intrarenal hemodynamics is the resistive index (RI), which is calculated from blood flow velocities in vessels reflecting renovascular resistance. The RI increases in various disorders, such as acute renal transplant rejection, urinary tract obstruction, renal vein thrombosis and acute tubular necrosis [13, 14]. The RI is also correlated with arterio-arteriolosclerosis in kidney damage and is an independent predictor of renal disease progression [15, 16]. Hamano *et al.* [17] reported that RI was significantly higher in patients with type 2 diabetes and albuminuria than in patients without albuminuria. In addition, RI can predict the outcome of renal function in patients with type 2 diabetes, microalbuminuria and preserved renal function [18]. Furthermore, increased RI of the renal arteries is associated with the severity of systemic atherosclerosis, such as increased carotid IMT and aortic pulse wave velocity [12, 19].

Few studies have investigated the association between RI and microalbuminuria/albuminuria, with most studies conducted in diabetic patients [17, 20, 21]. Because microalbuminuria is considered a manifestation of endothelial dysfunction in both diabetic and nondiabetic patients [22–24], we hypothesized that RI may be correlated with microalbuminuria in nondiabetic adolescents and young adults. Therefore, this study aimed to investigate the relationship between the RI of the interlobar renal arteries and microalbuminuria in nondiabetic adolescents and young adults.

Materials and methods

Participants and study design in follow-up

From 1992 to 2000, the Chinese Foundation of Health in Taipei, Taiwan, conducted an annual urine screening campaign of 2 615 000–2 932 000 school-aged children in Grades 1 through 12 in Taiwan [25, 26]. A urine strip (Hemscomistix IV urine strip; Ames Division, Miles Lab, Elkhart, IN) was used for the screening. Children with positive results for proteinuria, glucosuria or hematuria on two tests underwent a third urine screening test and a general health checkup using the same protocol [25, 26]. A total of 103 756 school children received the health checkups and the third urine screen and also had complete data profiles after detailed data checking. Among these children, 9227 had elevated blood pressure (EBP) and 94 529 had normal blood pressure (BP) based on the American Heart Association criteria [27]. For convenience and to conserve study resources, we invited these students living in the Taipei area (1251 with EBP and 17 448 with normal BP) and in Taichung city (304 with EBP and 3055 with normal BP) to participate in follow-up studies (Figure 1). There were no significant differences in age or sex between selected subjects and nonselected subjects.

The first follow-up study

To investigate the effect of childhood EBP on later life, we conducted a follow-up study. From May 2006 through September 2008, we established a cohort of adolescents and young adults, based on a previous history of EBP or normal BP in childhood. This cohort was selected from the 1992 to 2000 nationwide mass urine screening of school children aged 6–18 years in Taiwan [25, 26].

In the first follow-up study, we mailed invitation letters to eligible students in the Taipei area and in Taichung city. About 3–5 days later, 12 well-trained assistants and nurses performed telephone interviews inviting these subjects for a follow-up health examination. No telephone interview contact was made with normotensive students. Among the 1555 subjects with EBP in childhood, 202 had changed their phone numbers, 109 had moved, 383 could not be contacted, 154 missed follow-up appointments/examinations, 263 did not respond and 97 refused to participate. Overall, 347 subjects with EBP in childhood completed the follow-up health examinations, resulting in a response rate of 49% (347/707). Among the 20 503 subjects with normal BP in childhood, 6783 were randomly contacted by mail, 393 had moved, 5732 did not respond and 17 refused to participate. Finally, 641 subjects with normal BP in childhood completed the follow-up health examinations, resulting in a response rate of 10% (641/6390) (Figure 1).

The second follow-up study

To further study the correlation among albuminuria, renal artery RI and other CV risk factors, we invited 147 nondiabetic subjects living in the Taipei area with different severities of albuminuria (macroalbuminuria, microalbuminuria and normoalbuminuria) to participate in a substudy of this cohort (790 subjects from Taipei) from October through December 2008. The response rate of this second survey was 70% of those receiving an invitation (70 subjects each in three groups, 210 subjects in total).

In this second screening, in addition to first morning urinalysis, each study subject was interviewed and examined by a physician, a blood sample was taken and their BP was measured. Blood was drawn in the morning after a 12-h overnight fast. If repeated urinalysis (including quantitative measurements) in the second screening was positive, these subjects

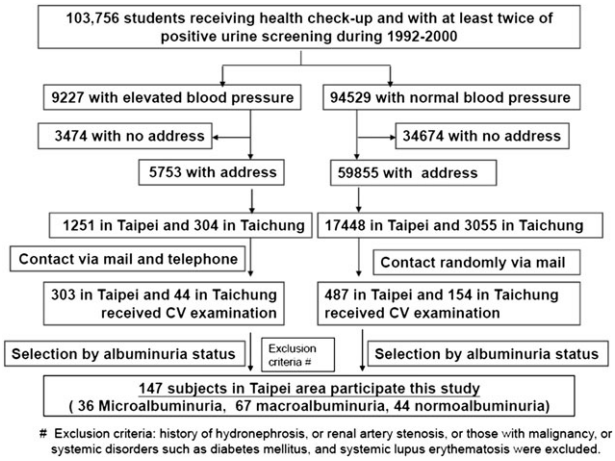

Fig. 1. Flow chart of the recruited participants.

were classified as having 10-year duration microalbuminuria/macroalbuminuria, and they were enrolled in the study. The mean duration of elapsed time from childhood to follow-up examination was 10.0 (5.8–14.7) years. Patients with known anatomical abnormalities, including a history of hydronephrosis or renal artery stenosis, or those with malignancy or systemic disorders, such as diabetes mellitus or systemic lupus erythematosus, were excluded from this study. Participants who had received steroid or hypertensive medication before the study enrollment were also excluded. The study protocol was approved by the Research and Ethics Committee of the National Taiwan University Hospital, and informed consent was obtained from all subjects. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration.

CV risk factors

Hypertension in children and adolescents is defined as average systolic blood pressure (SBP) and/or diastolic BP (DBP) that is more than or equal to the 95th percentile for gender, age and height on more than or equal to three occasions [27]. Subjects with SBP and/or DBP that is ≥140/90 mmHg, with a history of hypertension, or on anti-hypertension medication were considered as having hypertension if they were >18 years of age. Body mass index (BMI) for each subject was calculated by dividing their weight in kilograms by the square of their height in meters. Data on smoking habits and alcohol drinking were obtained from a structured questionnaire. Renal function expressed by the estimated glomerular filtration rate (eGFR) was calculated using the modified modification of diet in renal disease (MDRD) formula for Chinese patients: c-aGFR3 (mL/min/1.73 m^2) = 186 × $Pcr^{-1.154}$ × $age^{-0.203}$ × 0.742 (if female) × 1.233 (if Chinese) [28]. Insulin resistance status was estimated with the homeostasis model assessment (HOMA) index.

Urinary albumin measurements

Urinary albumin excretion was measured by enzyme-linked immunosorbent assay using first morning urine and was expressed in two ways: Urinary albumin concentration (UAC) and urinary albumin:creatinine ratio (ACR). Normoalbuminuria was defined as a urinary ACR <30 μg/mg. Microalbuminuria was defined as a urinary ACR ≥30 to 299 μg/mg, and macroalbuminuria was defined as a urinary ACR ≥300 μg/mg.

Duplex Doppler ultrasonography

Ultrasound examination was performed on subjects in a supine position after an overnight fast with a MicroMaxx system (SonoSite, Inc., Bothell, WA) with a 5-MHz convex array probe. A Doppler beam was placed on the tract of interlobar renal arteries. The RI was calculated using the following formula: RI = (peak systolic velocity − end-diastolic velocity)/peak systolic velocity. The RI was determined at least two times for the right and left kidneys and was averaged to obtain the mean RI for each subject. Thus, four measurements of RI were obtained from each subject. The presence of renal artery stenosis was excluded based on clinical findings and radiological examination of the kidney. Measurements were performed by two expert nephrologists who were unaware of any other information concerning the subjects. The intraobserver coefficients of variation were 3.0% and 3.6%, respectively. The interobserver coefficient of variation was 3.2%.

Carotid intima-IMT and brachial-ankle pulse wave velocity measurements

Carotid arteries were examined by a proficient technician using high-resolution B-mode ultrasonography. The IMT and atherosclerotic plaques at extracranial carotid arteries (ECCAs) were measured with a high-resolution B-mode ultrasonography, GE Vivid *i* ultrasound system (Horten, Norway), equipped with a 3.5-10 MHz real-time B-mode scanner. In addition, a software package for vascular ultrasound was applied for off-line automatic calculation after examination. Carotid atherosclerosis (CA) was assessed by IMT at carotid arteries and by ECCA plaque score using the measurement protocol for CA that has been described previously [29, 30]. The IMT was defined as the distance from the front edge of the first echogenic line (lumen–intima interface) to the front edge of the second line (media–adventitia interface) in the far wall of the vessel. The IMT was determined by averaging the measurement on both sides.

Aortic stiffness can be assessed noninvasively by measuring brachial-ankle pulse wave velocity (baPWV) [31, 32]. The baPWV was automatically calculated using a waveform analyzer (Colin VP2000; Omron Inc., Kyoto, Japan), which simultaneously recorded the following: (i) right and left brachial and tibial arterial pressure waveforms (ii) lead I of the electrocardiogram, and (iii) a phonocardiogram. The distance between the arm and ankle was automatically calculated based on the subject's height. Finally, the baPWV was calculated by dividing the distance with the time difference [31].

Statistical analysis

Statistical analyses were performed using SAS software (Version 9.1.3; SAS Institute Inc., Cary, NC, USA). Continuous variables were described by mean ± standard deviation (SD). Continuous variables were compared between groups using the Student's two-tailed *t*-test or the Mann–Whitney *U*-test if not normally distributed. The chi-square test was applied for categorical data. One-way analysis of variance (ANOVA) was used for multiple comparisons of more than three groups, followed by Schaffer's test. We did not test the correlation between RI and other indices of preclinical atherosclerosis (baPWV and carotid IMT) because of beyond the main research focus. Statistical analyses with linear mixed regression models were performed to determine the determinant variables for RI. The SAS procedure MIXED was used to fit linear models with repeated measures data (Rt_RI_1 Rt_RI_2 Lt_RI_1 Lt_RI_2). The adequacy of the predictive models was assessed using Akaike information criterion (AIC) weights. The model with the minimum AIC was regarded as the best model. The two-tailed P-value of <0.05 was considered to be statistically significant.

Results

A total of 147 subjects were enrolled in the cohort study: 67 with macroalbuminuria, 36 with microalbuminuria and 44 with normoalbuminuria (Table 1). Demographic data showed that males predominated (59.7%) in the macroalbuminuria group. The mean SBP and DBP showed between-group differences, with the microalbuminuria group having the lowest BP.

The BMI, waist circumference, fasting glucose, HOMA index, serum levels of total cholesterol, triglycerides, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), creatinine and eGFR did not differ significantly among the three groups. The macroalbuminuria group had the lowest high-density lipoprotein (HDL) level compared with the microalbuminuria and normoalbuminuria groups (P = 0.029). Mean RI were similar for subjects in the three groups (mean RI of ~0.60, P = 0.959). Mean carotid IMT was significantly higher in the macroalbuminuria group

(0.478 ± 0.060 mm) compared with the microalbuminuria and normoalbuminuria groups (P = 0.025). However, measurements of aortic pulse wave velocity (baPWV) did not differ among these three groups.

When study subjects were further stratified by the presence or absence of EBP in childhood, 72 subjects had EBP in childhood and 75 subjects had normal BP in childhood (Table 2). The EBP in childhood group had higher SBP, DBP and BMI and larger waist circumferences. There were no significant differences in the serum levels of total cholesterol, ApoA1, ApoB, glucose and HOMA index between the two groups, while higher low-density lipoprotein and lower HDL were noted in the EBP in childhood group. The serum creatinine levels of the two groups were similar, whereas the mean eGFR, as calculated by the modified MDRD formula, was higher in the EBP in childhood group (P = 0.003). Urinary albumin excretion, represented by either UAC or ACR, showed no significant differences between the two groups. There were also no significant differences in RI, carotid IMT or baPWV between the two groups.

The correlation between RI and urine albumin excretion in each participant was plotted in Figure 2. Logarithmically transformed urinary albumin excretion, represented by either log (urinary albumin concentration) or log (urinary ACR), did not correlate with RI.

We further analyzed the relationship between RI and determined variables using linear mixed regression models, and these models were compared with the AIC (Table 3). Only male gender and DBP were significantly associated with RI, while there was no significant association of RI with UAC (P = 0.924), ACR (P = 0.683) or EBP in childhood (P = 0.784). DBP is a significant independent determinant of RI.

Discussion

In the present study, we showed that renal vascular resistance was not significantly different between adolescents and young adults having macroalbuminuria or microalbuminuria compared with those having normoalbuminuria. A similar result was also found in children with insulin-dependent diabetes mellitus showing that there were no significant differences between the mean RI value in subjects with or without microalbuminuria [33]. Additionally, in patients with idiopathic chronic glomerulonephritis, RI was not correlated with proteinuria [16]. However, in contrast to our results, previous studies in adult diabetic patients showed that the mean RI was significantly higher in patients with microalbuminuria compared to those without microalbuminuria [17, 21]. In patients with essential hypertension, RI was positively correlated with albuminuria [34]. When RI is elevated, it may be used as a predictor in patients with advanced clinical diabetic nephropathy; however, it is often normal and thus not a prognostic predictor in the early clinical stages of diabetes mellitus [18, 21, 35].

We also observed a relationship between RI and traditional CV risk factors. In this study, RI correlated with

Table 1. Clinical characteristics of the study population categorized according to normoalbuminuria, microalbuminuria or macroalbuminuria[a]

Characteristics	Normoalbuminuria, $N = 44$	Microalbuminuria, $N = 36$	Macroalbuminuria, $N = 67$	P-value
Age (years)	22.2 ± 3.1	22.0 ± 3.7	21.3± 3.7	0.396
Male (%)	18 (40.9%)	11 (30.6%)	40 (59.7%)	0.012
BMI (kg/m^2)	22.0 ± 4.4	21.5 ± 4.8	21.7 ± 4.4	0.866
Waist (cm)	71.1 ± 10.7	70.4 ± 13.4	73.00 ± 12.5	0.529
SBP (mmHg)	117.4 ± 11.3	110.4 ± 12.5	116.4 ± 15.5	0.046
DBP (mmHg)	70.3 ± 7.3	65.4 ± 6.6	68.4 ± 9.6	0.033
Glucose (mmol/L)	4.93 ± 1.14	4.81 ± 0.84	4.79 ± 0.67	0.680
HOMA	3.00 (2.64–7.94)	2.88 (2.71–2.98)	2.95 (2.74–3.32)	0.464
Creatinine (mg/dL)	0.9 (0.8–1.1)	0.9 (0.8–1.0)	1.0 (0.9–1.1)	0.077
eGFR (mL/min/1.73 m^2)[b]	98.09 ± 21.91	96.33 ± 28.44	95.87 ± (26.19)	0.902
UAC (mg/L)[c]	6.25 (5.00–10.00)	12.15 (5.00–24.4)	14.80 (8.00–54.30)	<0.001
	8.85 ± 5.81	18.05 ± 19.50	77.75 ± 164.19	0.0026
ACR (mg/g)[c]	6.07 (3.64–7.77)	9.11 (5.74–22.27)	7.30 (4.69–25.41)	0.004
	6.42 ± 3.12	14.85 ± 12.56	88.16 ± 289.46	0.0583
RI	0.603 ± 0.043	0.604 ± 0.060	0.601 ± 0.048	0.959
Carotid IMT (mm)	0.435 ± 0.037	0.435 ± 0.028	0.478 ± 0.060	0.025
baPWV (cm/s)	1202.85 ± 115.64	1157 ± 160.16	1181.67 ± 145.96	0.360
CHO (mmol/L)	4.34 ± 0.70	4.45 ± 0.82	4.32 ± 0.84	0.744
TG (mmol/L)	0.81 (0.65–1.08)	0.76 (0.59–02)	0.96 (0.67–1.35)	0.155
HDL (mmol/L)	1.30 ± 0.32	1.35 ± 0.35	1.20 ± 0.23	0.029
LDL (mmol/L)	2.43 ± 0.67	2.31 ± 0.81	2.39 ± 0.80	0.766
ApoA1 (mg/dL)	141.3 ± 20.4	133.9 ± 29.9	133.0 ± 19.9	0.198
ApoB (mg/dL)	75.6 ± 16.0	80.1 ± 16.3	81.0 ± 21.3	0.386
Smoking habit (%)	8 (18.2%)	5 (13.9%)	7 (10.5%)	0.508
Alcohol habit (%)	5 (11.4%)	4 (11.1%)	5 (7.5%)	0.768

[a]CHO, cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol. Values are numbers (percentages) for categorical variables and means ± SDs for continuous variables, except for HOMA, creatinine, UAC, ACR and triglycerides, which are expressed as median (range).

[b]eGFR was calculated using the modified MDRD formula for Chinese patients. Alcohol habit indicated an alcohol use of 30 mL of alcohol per day at least 3 days/week.

[c]UAC and ACR are presented in two ways: means ± SD, median (range).

Table 2. Clinical characteristics of the study subjects stratified by elevated or normal BP in childhood[a]

Characteristics	Elevated BP in childhood, $N = 72$	Normal BP in childhood, $N = 75$	P-value
Age (years)	22.0 ± 3.7	21.5 ± 3.3	0.394
Male (%)	38 (52.8%)	31 (41.3%)	0.165
BMI (kg/m^2)	23.6 ± 4.8	20.0 ± 3.3	<0.001
Waist (cm)	75.8 ± 12.8	67.9 ± 10.2	<0.001
SBP (mmHg)	120.1 ± 14.2	110.6 ± 11.8	<0.001
DBP (mmHg)	70.6 ± 9.3	65.9 ± 6.9	0.001
Glucose (mmol/L)	4.92 ± 1.07	4.76 ± 0.62	0.277
HOMA	3.00 (2.64–7.96)	2.88 (2.74–3.08)	0.217
Creatinine (mg/dL)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	0.069
eGFR (mL/min/1.73 m^2)	103.03 ± 28.02	90.52 ± 21.07	0.003
UAC (mg/L)	9.85 (5.00–23.65)	11.70 (5.50–21.20)	0.571
ACR (mg/g)	6.76 (4.45–17.37)	6.99 (4.98–14.47)	0.619
RI	0.596 ± 0.049	0.607 ± 0.051	0.265
Carotid IMT (mm)	0.444 ± 0.045	0.449 ± 0.043	0.826
baPWV (cm/s)	1204.07 ± 142.84	1160.52 ± 137.21	0.063
CHO (mmol/L)	4.47 ± 0.82	4.25 ± 0.75	0.095
TG (mmol/L)	0.89 (0.69–1.33)	0.81 (0.59–1.11)	0.049
HDL (mmol/L)	1.21 ± 0.29	1.32 ± 0.29	0.021
LDL (mmol/L)	2.53 ± 0.77	2.24 ± 0.72	0.020
ApoA1 (mg/dL)	136.4 ± 24.9	136.1 ± 17.0	0.947
ApoB (mg/dL)	80.4 ± 18.3	75.9 ± 18.9	0.239
Smoking habit (%)	10 (13.9%)	10 (13.3%)	0.922
Alcohol habit (%)	7 (9.7%)	7 (9.3%)	0.936

[a]CHO, cholesterol; TG, triglycerides; LDL, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B.

age, male gender, SBP and DBP but did not correlate with other CV risk factors. In accordance with previous studies, independent variables for RI were the patient's age and BP [17, 21, 36]. This was similar to a study by Hamano *et al.* [17] in which DBP, but not SBP, was more significantly associated with RI. In contrast to previous studies observing a correlation between RI and creatinine clearance, such a result was not found in the present study [19, 21, 37]. The RI was independently and positively associated with insulin resistance in patients with newly diagnosed type 2 diabetes and essential hypertension [38]. Nevertheless, a relationship between RI and insulin resistance was not found in adolescents and young adults in the current study.

Furthermore, renal RI has been used to assess the severity of target organ damage in patients with hypertension [34]. Several studies in adult patients with essential hypertension and diabetes demonstrated that increased RI of the renal arteries is associated with the severity of systemic atherosclerosis and arterial stiffness as measured by carotid IMT and/or baPWV [12, 17, 19, 21]. Ohta *et al.* [19] found that PWV was independently associated with RI. Our results are consistent with previous studies where a significantly higher carotid IMT was observed in subjects with macroalbuminuria rather than with normoalbuminuria or microalbuminuria, which supports evidence of accelerated atherosclerosis in subjects with prominent macroalbuminuria.

In this study, regardless of a subject's extent of albuminuria, most parameters associated with CV risk factors did not show significant differences. Rademacher *et al.* [3] found that albuminuria excretion rates were not significantly related to age, BMI, insulin resistance or metabolic syndrome (BMI, SBP, triglycerides, HDL-C) in normal adolescents. In regard to predictors of albuminuria in normal

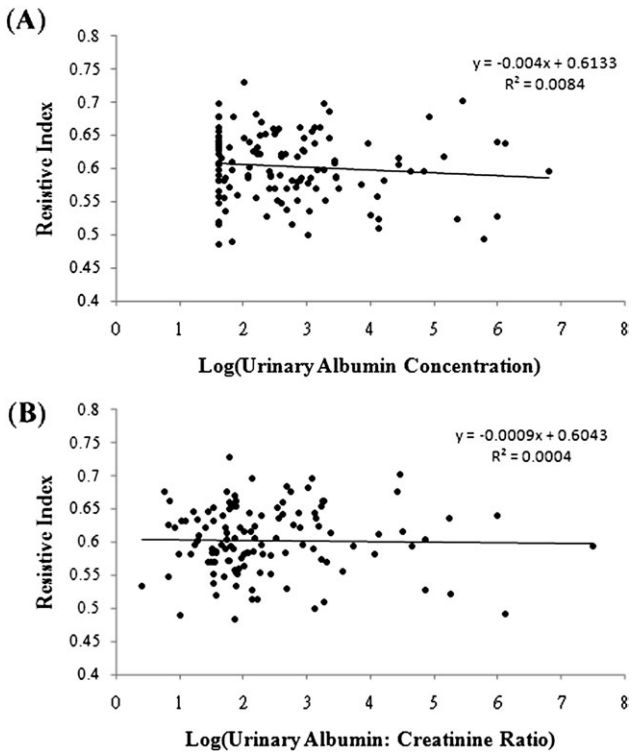

Fig. 2. Correlation between (**A**) RI and log (urinary albumin concentration) (mg/L) (**B**) RI and log (urinary ACR) (mg/g).

adolescents, previous studies have shown quite diverse results and have been summarized by Rademacher *et al.* [3].

Some mechanisms might explain why RI is not correlated with albuminuria in adolescents and young adults. First, though microalbuminuria may be a marker of

Table 3. Mixed regression models for the determinants of renal artery RI

Determinants	Model 1 β	P	Model 2 β	P	Model 3 β	P	Model 4 β	P	Model 5 β	P	Model 6 β	P	Model 7 β	P
Age (years)	−0.0031 (0.0012)	0.012	−0.0029 (0.0012)	0.017	−0.0025 (0.0012)	0.044	−0.0010 (0.0013)	0.445	−0.0010 (0.0013)	0.462	−0.0010 (0.0013)	0.468	−0.0009 (0.0013)	0.476
Sex (male)			−0.0261 (0.0085)	0.003	−0.0167 (0.0109)	0.127	−0.0265 (0.0111)	0.019	−0.0264 (0.0112)	0.020	−0.0262 (0.0112)	0.021	−0.0265 (0.0113)	0.021
SBP (mmHg)					−0.0006 (0.0004)	0.168	0.0011 (0.0008)	0.158	0.0011 (0.0008)	0.159	0.0011 (0.0008)	0.165	0.0011 (0.0008)	0.160
DBP (mmHg)							−0.0029 (0.0011)	0.007	−0.0030 (0.0011)	0.008	−0.0030 (0.0011)	0.007	−0.0030 (0.0011)	0.007
UAC (mg/L)									0.00000 (0.00004)	0.924	—	—	—	—
ACR (mg/g)											0.00001 (0.00003)	0.692	0.00001 (0.00003)	0.683
EBP in childhood													−0.0025 (0.0092)	0.784
AIC	−1418.7		−1420.0		−1408.3		−1403.7		−1835.3		−1384.6		−1377.1	

EBP, elevated blood pressure; AIC, Akaike information criterion.

endothelial dysfunction, RI may not. A recent study by Raff *et al.* [39] showed no evidence to support the idea that renal RI is a useful tool to test renal endothelial function in humans. Second, endothelial dysfunction was thought to be an early event of atherosclerosis, manifested as microalbuminuria, while elevated RI may represent a late event in atherosclerosis, which was rarely observed in our study subjects. Thus, the present study indicates that younger age groups (like our subjects) may have had too short a duration to develop a significant difference in arterial RI in their renal artery. Third, the underlying pathophysiology of microalbuminuria may differ in nondiabetic adolescents and young adults. While microalbuminuria in adults is a sign of atherosclerosis and is a CV risk factor, microalbuminuria in nondiabetic children may be due to idiopathic chronic glomerulonephritis and thus related to glomerular arteriolosclerosis alone, without correlating to systemic atherosclerosis and CVD risk [16].

The adolescents and young adults in our study were invited to participate in this study based on random samples from previous mass screening of school students. As most subjects were relatively healthy and did not receive a renal biopsy, the underlying diseases and pathophysiology of their albuminuria were unclear. Nevertheless, Lin *et al.* [40] has conducted renal biopsies in selected children with positive urinary screening in Taiwan, which identified orthostatic proteinuria as the most important underlying disease in children with light proteinuria (30–100 mg/dL), while various types of primary and secondary glomerulonephritis were the major causes in children with heavy proteinuria (>100 mg/dL). Regarding microalbuminuria, with the exception of early stages of other glomerular diseases, the cause of nondiabetic microalbuminuria in adults has been related to hypertension and metabolic syndrome [41]. The prevalence rates of microalbuminuria in hypertensive patients are higher than in the general population [42]. However, in this study comparing the microalbuminuria group with the normoalbuminuria group, there was no significant difference in components of metabolic syndrome. Thus, although albuminuria is a valuable marker for CVD in adults, more research is warranted to answer the prognostic significance of albuminuria in children [43].

Our study has some limitations. Younger children may have lower muscle mass and, therefore, lower creatinine excretion [44], which for a given level of albumin excretion will increase the prevalence of microalbuminuria. Secondly, the underlying diseases and pathophysiology of albuminuria were not determined because it was difficult to convince patients without nephritic-range albuminuria to participate in an invasive study. Thirdly, as there were no quantitative data of initial measurements of daily protein loss for each student, the status of their progression or regression was not accessible. This combination of the progression and regression data may conceal the clinical significance of RI in this population. Fourthly, the number of subjects in this study was small.

In conclusion, renal artery RI is not correlated with urinary albumin excretion in nondiabetic adolescents and young adults.

Acknowledgements. This study was supported by grants from National Health Research Institute of Taiwan (NHRI-EX97-9721PC, EX97-9821PC, and EX97-9921PC) and (NHRI-EX95-9531PI, EX95-9631PI, and EX95-9731PI).

Conflict of interest statement. None declared.

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Received for publication: 27.6.10; Accepted in revised form: 21.2.11