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URINE ALBUMIN CREATININE RATIO IS ASSOCIATED WITH CAROTID ATHEROSCLEROSIS IN A COMMUNITY BASED COHORT: ATHEROSCLEROSIS RISK OF RURAL AREA IN KOREAN GENERAL POPULATION STUDY

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BACKGROUND: Albuminuria is a surrogate marker of endothelial dysfunction and a predictor of cardiovascular events. Data are limited with regard to the relationship between albuminuria and subclinical atherosclerosis in a community-based cohort. We determined the association between albuminuria measured by the urine albumin creatinine ratio (UACR) and carotid intima media thickness (CIMT) in a Korean rural population.

METHODS: We enrolled 1,369 healthy subjects older than 40 years (857 males and 518 females) with normal renal function and measured the CIMT. We excluded subjects with overt proteinuria (> 300 mg/day) or with treatment of diabetes mellitus, hypertension, dyslipidemia, and any cardiovascular disease. The subjects were stratified into the quartile value of the UACR (lowest quartile: UACR < 4.8 and highest quartile: UACR > 17.7). And we evaluate the relationship between UACR and CIMT by linear regression and logistic regression analysis.

RESULTS: Increasing quartile of the UACR had a stepwise increase in body mass index, blood pressure, cholesterol profile [low density lipoprotein (LDL)-cholesterol and triglyceride], glucose, homeostratic model assessment of insulin resistance (HOMA-IR), and C-reactive protein (all p values < 0.001). Maximal CIMT from the 1^{st} to the 4^{th} quartile values of the UACR were 0.74 ± 0.17, 0.77 ± 0.18, 0.78 ± 0.18, and 0.82 ± 0.21 mm, respectively ($p < 0.001$). In a multivariate regression model adjusted for age, sex, systolic blood pressure, triglyceride, LDL-cholesterol, fasting blood sugar, waist circumference, adiponectin, HOMA-IR, high sensitive C-reactive protein, smoking, UACR showed a significant association with maximal CIMT (B = 0.014, $R^2 = 0.145$, $p = 0.002$).

CONCLUSION: Albuminuria measured by the UACR was significantly associated with both CIMT and traditional risk factors of atherosclerosis except for smoking in healthy Koreans.

KEY WORDS: Urine albumin creatinine ratio · Carotid intima-media thickness.

INTRODUCTION

The association between chronic kidney disease as estimated by glomerular filtration rate and cardiovascular disease is well-established.[1)] However, recent data suggests that urinary

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albumin excretion (UAE), especially low-grade albuminuria, has an important role in cardiovascular mortality.[2] The association between UAE and atherosclerotic vascular disease has usually been studied in diabetic patients as a predictor of cardiovascular disease, kidney involvement, and mortality.[3,4] However, recent data involving healthy individuals without diabetes or hypertension has demonstrated that the risk of cardiovascular events increase continuously with the level of UAE, even in subjects who fall below the threshold for the definition of microalbuminuria based on the Framingham heart study.[5] In addition, UAE predicted the progression of atherosclerosis in a non-diabetic population-based study.[6,7] However, the association between UAE and progression of atherosclerotic disease in a south-east Asian population is less well-established. The aim of this study was to determine the relationship between UAE measured by the urine albumin creatinine ratio (UACR) and carotid intima media thickness (CIMT) in a healthy rural population.

Methods

Study population

The atherosclerosis risk of a rural area Korean general population (ARIRANG) study is an ongoing study of cardiovascular and metabolic risk factors that is being conducted in the rural area of Wonju, Gangwon-do, Korea. The ARIRANG study was approved by the Ethics Committee of the Wonju Christian Hospital of Wonju College of Medicine, Yonsei University (Wonju, Gangwon-do, Korea, approval number: CR105024), and written informed consent was obtained from all study participants. In the present study, we enrolled 1,369 healthy subjects older than 40 years of age (857 males and 518 females) with normal renal function and measured the CIMT.

We excluded subjects with overt proteinuria (> 300 mg/day) or patients under treatment for diabetes mellitus, hypertension, dyslipidemia, or any cardiovascular disease.

Clinical evaluation and laboratory methods

All participants underwent a complete evaluation following 8 hours of fasting, which included the following: (1) history, physical examination, and anthropometric analysis; (2) measurement of heart rate and blood pressure (measured after 10 minutes resting in a sitting position, was expressed as the average of 3 consecutive measurements taken from each arm); (3) measurement of fasting blood sugar (FBS) and insulin levels, and calculation of homeostatic model assessment of insulin resistance (HOMA-IR) [(fasting glucose × fasting insulin)/22.5]; (4) measurement of fasting plasma lipids [i.e., concentrations of triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and low-density lipoprotein cholesterol (LDL-C)]; (5) measurement of high sensitive C-reactive protein (hs-CRP); and (6) urinary albumin (mg/dL) and creatinine (mg/dL) were measured from a spot urine sample. For the analysis of this study, the UACR was calculated.[8]

Measurement of CIMT

Measurement was performed using a validated procedure, as described previously.[9]

An ultrasound system (Vivid-7; General Electric-Vingmed, Milwaukee, WI, USA) and a phased array 12-MHz transducer were used to obtain a high-resolution B-mode ultrasound view of the far wall of the common carotid artery. The common carotid arteries were explored, starting from a position 1 cm below the flow divider and between the internal and external carotid arteries. Measurements were taken by tracing the leading edge of the lumen-intima and the media-adventitia interfaces in plaque-free areas. Carotid atherosclerosis was defined as ≥ 0.9 mm of peak CIMT in both genders according to the joint European Society of Hypertension (ESH)/Europeans Society of Cardiology (ESC) guidelines.[10]

Statistical analysis

Statistical analysis was performed using SPSS 12.0 software (SPSS Inc., Chicago, IL, USA). The subjects were stratified into quartile values of the UACR. The lowest quartile of the UACR was < 4.8, and the highest quartile of the UACR was > 17.7. Continuous variables are presented as the mean ± SD or median (interquartile range), and categorical variables as absolute numbers or percentages. The levels of CRP, TG, and HOMA-IR were log-transformed. Chi-square statistical analysis was used to determine the difference in categorical variables between the quartile groups of the UACR. Analysis of variance (ANOVA) was used to determine differences in continuous variables. A Kruskal-Wallis test was used in log-transformed continuous variables.

Logistic regression analysis was performed using the UACR quartile groups to examine the scale of the association between the UACR and carotid atherosclerosis. Also, the association between the UACR with carotid atherosclerosis was tested by means of linear regression and logistic regression analysis. Multivariate regression analysis was adjusted, as follows: (1) model I: age, sex; (2) model II: age, sex, systolic blood pressure, TG, LDL-cholesterol, FBS, waist circumference; (3) model III: age, sex, systolic blood pressure, TG, LDL-cholesterol, FBS, waist circumference, adiponectin, HOMA-IR, hs-CRP, smoking (yes or no). Regression coefficients and odd ratio (OR) were calculated for a 1-unit increase in the log-transformed UACR.

Table 1. Basal demographic and metabolic characteristics

	1st quartile (n = 343)	2nd quartile (n = 341)	3rd quartile (n = 343)	4th quartile (n = 342)	*p* value
UACR range (mg/dL/mg/dL)	≤ 4.8	≤ 9.1	≤ 17.7	> 17.7	
Age (yrs)	51.6 ± 7.7	52.9 ± 7.9	54.6 ± 8.0	55.8 ± 8.0	< 0.001
Male, n (%)	282 (30)	240 (25.5)	195 (20.7)	224 (23.8)	< 0.001
BMI (kg/m^2)	23.9 ± 2.8	24.1 ± 3.0	24.4 ± 2.9	25.1 ± 3.6	< 0.001
Waist circumference (cm)	81.3 ± 9.0	82.1 ± 3.0	83.7 ± 8.6	86.1 ± 8.8	< 0.001
Current smoker, n (%)	57 (16.6)	60 (17.7)	47 (14.0)	57 (16.8)	0.542
SBP (mmHg)	129.4 ± 17.1	128.6 ± 16.1	129.1 ± 18.9	134.9 ± 21.8	< 0.001
DBP (mmHg)	78.1 ± 11.0	80.3 ± 10.6	81.6 ± 12.7	84.8 ± 12.4	< 0.001
TG (mg/dL)*	126.2 ± 27.2	136.3 ± 90.2	144.9 ± 91.0	165.0 ± 107.4	< 0.001
HDL-cholesterol (mg/dL)	44.9 ± 10.9	46.1 ± 10.4	47.7 ± 11.8	47.7 ± 11.5	0.001
LDL-cholesterol (mg/dL)	112.1 ± 27.2	115.9 ± 32.3	119.9 ± 33.2	121.7 ± 32.8	< 0.001
FBS (mg/dL)	93.7 ± 10.1	91.4 ± 9.5	91.9 ± 12.7	95.5 ± 18.1	< 0.001
hs-CRP (mg/L)*	0.5 (0.2 - 1.0)	0.63 (0.3 - 1.5)	0.7 (0.4 - 1.6)	0.9 (0.5 - 1.8)	< 0.001
HOMA-IR*	2.1 (1.5 - 2.6)	1.7 (1.4 - 2.3)	1.8 (1.4 - 2.3)	1.9 (1.5 - 2.7)	0.002
IMT max (mm)	0.74 ± 0.17	0.77 ± 0.18	0.78 ± 0.18	0.82 ± 0.21	< 0.001

Values are presented as mean ± SD. *log transformed values which are presented as median (1st quartile - 3rd quartile), and *p* value are measured by Kruskal Wallis test. UACR: urine albumin-creatinine ratio, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, FBS: fasting blood sugar, hs-CRP: high sensitive C-reactive protein, HOMA-IR: homeostatic model assessment of insulin resistance, IMT max: maximal intima media thickness

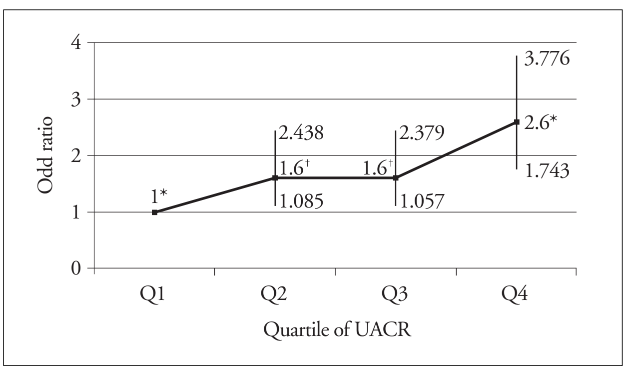

Fig. 1. Odd ratios of carotid atherosclerosis according to quartile groups of UACR. *$p < 0.001$, †$p < 0.05$. UACR: urine albumin creatinine ratio.

RESULTS

BASAL DEMOGRAPHIC AND METABOLIC CHARACTERISTICS

Table 1 shows the clinical characteristics and vascular risk factors of the entire study population according to quartiles of the UACR. Age, body mass index (BMI), waist circumference, TG, LDL-cholesterol, and hs-CRP increased across the UACR quartile groups (all *p* for trend < 0.001). The overall median the CIMT was 0.74 mm (interquartile range 0.64 - 0.87 mm). The thickness of maximal CIMT was steadily increased across quartile groups for the UACR (0.74 ± 0.17, 0.77 ± 0.18, 0.78 ± 0.18, and 0.82 ± 0.21 mm, respectively, *p* for trend < 0.001)(Table 1).

UACR QUARTILE AND THE RISK OF CAROTID ATHEROSCLEROSIS

Each increase in quartile of the UACR was associated with carotid atherosclerosis. The OR of carotid atherosclerosis increased steadily to across quartile groups of the UACR (Fig. 1).

After adjustment for age and sex (model I), a significant association was shown between the increase in the UACR quartile and the increase in the maximal CIMT (Table 2 and 3). Based on multivariable analysis by linear regression method of model II, the statistical significance between UACR and maximal CIMT was remained ($p = 0.01$)(Table 2). However, multivariable logistic regression analysis of model II, the association decreased in strength with no statistical significance (Table 3). In the model III, the UACR still remained as a significant predictor for increased CIMT after adjustment for various clinical risk factors (Table 2 and 3).

DISCUSSION

The main finding of this study is that albuminuria measured by UACR is significantly associated with increase of CIMT in general rural healthy subjects.

In the strong heart study which included diabetes mellitus patients, albuminuria was independently associated with left ventricular systolic and diastolic dysfunction, and extent this results, albuminuria was also associated with increased cardiovascular death.[11)] Microalbuminuria was also associated with ischemic heart disease (IHD) in 2,085 subjects who had no IHD, renal disease, and diabetes mellitus.[12)] Atherosclerosis of coronary artery was significant higher as 2.2-fold in elevated UAE subjects.[13)] Despite the large body of evidences of relationship between UAE and cardiovascular disease, the reports related to the atherosclerosis and UAE in general healthy population is not so many. Jørgensen et al.[6)]

Table 2. Association of urine albumin creatinine ratio with atherosclerosis of carotid artery by linear regression analysis

	B	R^2	SE	*p* value
Model I	0.017	0.117	0.004	< 0.001
Model II	0.011	0.139	0.004	0.01
Model III	0.014	0.145	0.004	0.002

Analyzed using single linear regression analysis. Regression coefficients were calculated for a 1-unit increase in log-transformed urine ACR. Model I: adjusted for age, sex; model II: adjusted for age, sex, SBP, LDL-cholesterol, FBG, waist circumference; model III: adjusted for age, sex, SBP, TG, LDL-cholesterol, FBS, waist circumference, adiponectin, HOMA-IR, hs-CRP, current smoking. B: non-standardized regression coefficient, SE: standard error, abbreviations are discussed in table 1

Table 3. Association of urine albumin creatinine ratio with atherosclerosis of carotid artery by logistic regression analysis

	OR	95% CI	*p* value
Model I	1.202	1.066 - 1.355	0.002
Model II	1.122	0.991 - 1.270	0.06
Model III	1.161	1.021 - 1.320	0.02

Analyzed using logistic regression analysis. Odd ratio was calculated for a 1-unit increase in log-transformed urine ACR. Model I: adjusted for age, sex; model II: adjusted for age, sex, SBP, LDL-cholesterol, FBS, waist circumference; model III: adjusted for age, sex, SBP, TG, LDL-cholesterol, FBG, waist circumference, adiponectin, HOMA-IR, hs-CRP, current smoking. OR: odd ratio, 95% CI: 95% confidence interval, abbreviations are discussed in table 1

demonstrated the risk of developing atherosclerotic plaque correlated with baseline albuminuria rate, increasing across the spectrum of low grade albuminuria. Furtner et al.[7] also showed UAE was significantly related to atherosclerosis in general healthy population. However, to the best of our knowledge, no study has been publised on the relation between microalbuminuria and atherosclerosis of the carotid artery in Korean healthy population. There is a still controversal issue for independent association between UACR and atherosclerosis. Recent study showed that significant association was lost between UACR and atherosclerosis after adjustments of traditional risk factors such as blood pressure, waist hip ratio, and age.[14] Our results showed no statistically significance between UACR and atherosclerosis in a model II by the logistic regression analysis, however, after adding additional risk factors such as TG, adiponectin, HOMA-IR, hs-CRP, current smoking, the UACR still remained as a significant predictor for increased CIMT. These additional risk factors play as a compounding variable. When we exclude these compounding variables, the relationship between UACR and CIMT were clear (Table 3).

The mechanism of independent relation between UAE and atherosclerosis have been suggested that impairment of endothelial function and low-grade chronic inflammation. That is, albumin leakage into the urine is a reflection of widespread of the vascular damage, especially kidney. However, there is controversy about the explanation of this mechanism. Agewall and Björn[14] showed increased UAE, endothelial dysfunction, and chronic inflammation was interrelated processes to develop atherosclerosis in type 2 diabetic patient. Other studies indicated that although microalbuminuria, endothelial dysfunction, and low grade inflammation were linked together, they were independently associated with risk for cardiovascular death.[15] Although our data did not show the relationship between endothelial dysfunction and UAE, the result of the relationship between UACR and atherosclerosis remained significantly was implied that UAE might be a one of independent factor to be carotid atherosclerosis. Further studies will need to address the exact relationship and interrupted factors between UAE and atherosclerosis.

In conclusion, albuminuria measured by UACR is significantly associated with traditional risk factors of atherosclerosis except for smoking. Furthermore, microalbuminuria is the independent factor for carotid atherosclerosis after adjustment of these important clinical risk factors in Korean healthy individuals.

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