Association between Albuminuria, Carotid Atherosclerosis, Arterial Stiffness, and Peripheral Arterial Disease in Korean Type 2 Diabetic Patients

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Key Words

Albuminuria · Arterial stiffness · Carotid atherosclerosis · Korean type 2 diabetic patients · Peripheral arterial disease

Abstract

Background: To evaluate the association between albuminuria, carotid atherosclerosis, arterial stiffness, and peripheral arterial disease (PAD) in Korean type 2 diabetic patients.

Methods: In total, 673 type 2 diabetic patients registered with the public health center participated. Following an overnight fast, venous blood and urine samples were collected and analyzed. The carotid intima-media thickness (IMT), amount of carotid plaque, brachial ankle pulse wave velocity (baPWV), and the ankle-brachial index of each patient were also assessed. **Results:** Albuminuria was significantly associated with PAD (odds ratio (OR) 2.33; 95% confidence interval (CI) 1.28–4.25 for normoalbuminuria vs. microalbuminuria and OR 3.28; 95% CI 1.40–7.66 for normoalbuminuria vs. macroalbuminuria), but not with carotid plaque. The mean baPWV differed significantly according to the level of albumin relative to the creatinine ratio (1,764.79,

1,778.98, and 2,001.33, respectively; $p < 0.001$), while no significant difference was observed in the mean IMT value (0.73, 0.74, and 0.72, respectively; $p = 0.399$). **Conclusions:** Albuminuria was significantly associated with baPWV and PAD, but not with carotid plaque or CCA-IMT, in Korean type 2 diabetic patients.

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Introduction

In the 20th century, cardiovascular disease (CVD) became the main cause of mortality and morbidity in Western populations, and in 2000, the global prevalence of diabetes was estimated at 171 million [1]. The risk of coronary artery disease is six times higher in type 2 diabetes patients than in the general population [2, 3]. Therefore, the development of methods to estimate the risk of CVD in diabetes patients is highly desirable and will aid in preventing CVD incidence and lowering the disease burden of diabetes.

One of these measures, albuminuria, is correlated with cardiovascular mortality and morbidity, especially in high-risk groups, diabetic patients [4] and hypertensive patients [5]. It has also been reported that microalbuminuria and macroalbuminuria are predictors of mortality [6] and end-organ damage [7]. Because albuminuria is easily measurable, it can be broadly applied in the routine care of diabetic patients.

Many surrogate measures for CVD that estimate subclinical atherosclerosis have been developed. Carotid artery intima-media thickness (IMT) is known to be correlated with coronary artery disease, stroke, and several other risk factors [8–10]. Carotid plaque has different pathogenic characteristics to IMT; however, both IMT and carotid plaque share a common association with atherosclerosis and ischemic heart symptoms [11, 12]. The ankle-brachial index (ABI) is an easy method for measuring peripheral arterial disease (PAD), therefore ABI is commonly used to screen for PAD in diabetics [13]. Pulse wave velocity (PWV) has also been identified as a strong independent predictor of cardiovascular risk [14].

Many studies have evaluated the association between albuminuria and these surrogate measures [15–18]. Most researchers, however, have examined the association between albuminuria and only one or two variables. Therefore, it is difficult to generally assess the association between albuminuria and various subclinical atherosclerosis phenotypes.

In contrast to previous studies that only measured one or two variables, we measured the albumin to creatinine ratio (ACR), common carotid artery (CCA)-IMT, carotid plaque, brachial ankle PWV (baPWV), and ABI in our subjects and examined whether albuminuria would be correlated with carotid atherosclerosis, arterial stiffness, and PAD in Korean type 2 diabetic patients.

Subjects and Methods

Subjects

Among the 1,275 type 2 diabetes patients registered at the Public Health Center of Seo-gu, Gwangju, and Gokseng-gun, Jeollanamdo, Korea, 709 subjects with type 2 diabetes participated in this study. The response rate for this study was 55.5%. Ten patients who did not provide a blood sample and 26 patients who did not provide a urine sample were excluded from the study. After excluding these patients, a total of 673 patients participated in the study. This study was conducted in accordance with the Declaration of Helsinki guidelines. The study protocol was approved by the Institutional Review Board of Chonnam National University Hospital, and informed consent was obtained from each subject.

Methods

Well-trained examiners interviewed the patients using a survey that included questions on cigarette use, alcohol consumption, physical activity, antidiabetic medication use, antihypertension medication use, and CVD history.

Weight was measured to the nearest 0.1 kg while the subjects were dressed in light clothes and height was measured to the nearest 0.1 cm in stocking feet. Abdominal circumference was measured to the nearest 0.1 cm at expiration through a horizontal plane around the abdomen midway between the lowest rib and iliac crest. Blood pressure (BP) was measured twice using a standard mercury sphygmomanometer after the subjects had rested for at least 5 min. BP measurements were read to the nearest 2 mm Hg.

Following an overnight fast, venous blood was collected and the serum was separated on site and stored at -70°C until further analysis. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were analyzed using enzymatic methods. All sera were examined using an automatic analyzer (Hitachi-7600, Hitachi Ltd, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol was measured as proposed by Friedewald et al. [19], except when triglyceride levels exceeded 400 mg/dl. In such instances, the data were treated as missing.

Urinary albumin and creatinine concentrations were measured using a turbidimetric immunoassay and the Jaffe method [20] on an automated analyzer (Hitachi-7600, Hitachi Ltd). ACR was calculated by dividing the urinary albumin concentration in micrograms by the urinary creatinine concentration in milligrams. An ACR $<30.0\text{ }\mu\text{g/mg}$ creatinine was defined as normoalbuminuria, an ACR from 30 to $299.9\text{ }\mu\text{g/mg}$ creatinine was defined as microalbuminuria, and an ACR $\geq 300.0\text{ }\mu\text{g/mg}$ creatinine was defined as macroalbuminuria. The kidney function was ascertained by estimated glomerular filtration rate, which was calculated by the Modification of Diet in Renal Disease (MDRD) formula [21]:

$$186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 0.742 \text{ (if female),}$$

where serum creatinine concentration is in mg/dl.

Well-trained medical doctors performed ultrasonographic scans of the carotid arteries using high-resolution B-mode ultrasound (SonoAce 9900, Medison, Korea) with an electrical linear array transducer (7.5 MHz). IMT was defined as the distance from the leading edge of the first echogenic line to the second echogenic line, which indicated the media-adventitia interface. Images of the thickest point within 10 mm from the carotid bulb to the CCA were saved as CCA-IMT, and then measured using SigmaScan Pro Version 5.0.0 (SPSS Inc., Chicago, Ill., USA).

The examiners evaluated the CCA, carotid bulb, and internal carotid artery to determine the amount of carotid plaque. Protrusions into the lumen that were 100% thicker than the nearest area were defined as plaque. If the plaque was the thickest point, the distance to the nearest point without plaque was defined as the IMT.

After at least a 5-min rest, the ABI and baPWV were calculated automatically in the supine position using the VP-1000 system (Colin Co., Komaki, Japan) with cuffs around both arms and ankles. If any of the ABIs were <0.9 , the patient was defined as having PAD.

Table 1. General and biochemical characteristics

Variable	ACR, $\mu\text{g}/\text{mg}$ creatinine			Total	p value
	<30	30–299	≥ 300		
Number (%)	355 (52.7)	260 (38.6)	58 (8.6)	673 (100)	–
ACR, $\mu\text{g}/\text{mg}$ creatinine	16.0 ± 6.6	81.2 ± 59.6	876.1 ± 648.5	115.3 ± 304.4	<0.001
eGFR, $\text{ml}/\text{min}/1.73 \text{ m}^2$	66.1 ± 13.6	65.5 ± 17.2	55.6 ± 21.6	65.0 ± 16.1	<0.001
Male (%)	103 (29.0)	93 (35.8)	19 (32.8)	215 (31.9)	0.165
Age, years	67.7 ± 9.7	68.6 ± 10.2	68.9 ± 11.1	68.2 ± 10.0	0.470
Age at diabetic diagnosis, years	59.7 ± 11.7	59.5 ± 12.8	56.2 ± 14.2	59.3 ± 12.4	0.131
Diabetic duration, years	8.0 ± 7.6	9.1 ± 7.9	12.7 ± 10.2	8.9 ± 8.0	<0.001
Height, cm	154.8 ± 8.3	154.8 ± 8.9	154.0 ± 8.1	154.7 ± 8.5	0.799
Weight, kg	58.6 ± 9.8	58.6 ± 9.7	57.4 ± 11.1	58.5 ± 9.9	0.665
BMI	24.5 ± 3.9	24.5 ± 3.5	24.2 ± 4.1	24.5 ± 3.7	0.795
Abdomen circumference, cm	88.5 ± 9.3	89.3 ± 9.0	88.6 ± 11.0	88.8 ± 9.4	0.631
Systolic BP, mm Hg	126.8 ± 16.4	132.7 ± 17.4	141.8 ± 17.8	130.4 ± 17.5	<0.001
Diastolic BP, mm Hg	71.4 ± 9.4	72.6 ± 10.2	73.8 ± 10.6	72.1 ± 9.9	0.114
Total cholesterol, mg/dl	191.2 ± 42.2	196.3 ± 44.2	197.8 ± 52.9	193.7 ± 44.0	0.284
Triglycerides, mg/dl	176.6 ± 77.8	188.0 ± 107.0	195.5 ± 86.6	182.6 ± 91.0	0.168
HDL cholesterol, mg/dl	47.9 ± 11.7	47.3 ± 11.5	47.6 ± 12.6	47.6 ± 11.7	0.831
LDL cholesterol, mg/dl	108.1 ± 34.1	112.9 ± 34.5	111.0 ± 42.7	110.2 ± 35.1	0.246
Fasting plasma glucose, mg/dl	129.2 ± 45.8	144.7 ± 53.6	150.3 ± 55.7	137.0 ± 50.5	<0.001
HbA _{1c} , %	7.2 ± 1.6	7.8 ± 1.5	7.8 ± 1.9	7.5 ± 1.6	<0.001
CCA-IMT, mm	0.73 ± 0.15	0.75 ± 0.16	0.73 ± 0.15	0.74 ± 0.15	0.162
baPWV, m/s^a	$1,722.9 \pm 381.1$	$1,841.3 \pm 388.3$	$2,037.9 \pm 525.6$	$1,796.3 \pm 408.2$	<0.001
Current smoker (%)	52 (14.6)	43 (16.7)	11 (19.0)	106 (15.8)	0.334
Hypertension (%) ^b	241 (68.3)	194 (75.2)	52 (89.7)	487 (72.8)	0.001
Numbers of carotid plaques ≥ 1 (%)	157 (44.9)	131 (51.4)	33 (57.9)	321 (48.5)	0.030
Oral diabetics (%)	323 (96.4)	237 (91.9)	49 (86.0)	609 (93.7)	0.047
Insulin injection (%)	12 (3.6)	21 (8.1)	8 (14.0)	41 (6.3)	0.047
ABI ≤ 0.9 (%)	21 (6.0)	39 (15.1)	13 (22.4)	73 (10.9)	<0.001

Values are given as the mean $\pm$ SD or number (%). ACR = Albumin to creatinine ratio; eGFR = estimated glomerular filtration rate; BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; HbA_{1c} = glycated hemoglobin; CCA = common carotid artery; IMT = intima-media thickness; baPWV = brachial-ankle pulse wave velocity; ABI = ankle-brachial index.

^a Calculated with the patients with their ABI ≥ 0.9 after excluding the patients with ABI < 0.9 .

^b Hypertension was defined as systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg or taking antihypertension medication.

Statistics

Data are given as mean $\pm$ SD or percentage for categorical variables. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using the SPSS 15.0 software package (SPSS Inc.). Plaque was dichotomized according to the number of plaques (≤ 1 or > 1), while PAD was dichotomized according to the ABI value (≤ 0.9 or > 0.9). A logistic regression was used to provide odds ratios (ORs) for the categorical variables, i.e. carotid plaque and PAD, according to the ACR level (ACR < 30 , 30–300, and ACR ≥ 300 $\mu\text{g}/\text{mg}$ creatinine). An analysis of covariance was used to compare the means of the continuous variables, i.e. CCA-IMT and PWV, according to the ACR level. When we calculated PWV, we excluded any subjects that had ABIs < 0.9 or who had a history of CVD. We defined hypertension as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or taking antihypertension medication.

Results

General and Biochemical Characteristics

General and biochemical characteristics of the 673 subjects (215 men and 458 women) are detailed in table 1. 355 (52.7%) subjects had an ACR < 30 $\mu\text{g}/\text{mg}$ creatinine, 260 (38.6%) had an ACR between 30 and 300 $\mu\text{g}/\text{mg}$ creatinine, and 58 (8.6%) had an ACR ≥ 300 $\mu\text{g}/\text{mg}$ creatinine. Diabetic duration, systolic BP, fasting plasma glucose, HbA_{1c}, and baPWV tended to increase in groups with higher ACR levels. In contrast, estimated glomerular filtration rate tended to decrease in groups with higher ACR levels. Patients with higher ACR levels were more

Table 2. ORs for carotid plaque and PAD according to ACR level

	ACR, $\mu\text{g}/\text{mg}$ creatinine	Crude OR	Model 1 ^a	Model 2 ^b
Carotid plaque ^c	<30	1.00	1.00	1.00
	30–299	1.30 (0.94, 1.79)	1.21 (0.87, 1.69)	1.06 (0.74, 1.53)
	≥ 300	1.69 (0.96, 2.98)	1.61 (0.90, 2.89)	1.36 (0.72, 2.55)
	p for the trend	0.030	0.077	0.396
PAD ^d	<30	1.00	1.00	1.00
	30–299	2.78 (1.59, 4.85)	2.57 (1.46, 4.52)	2.33 (1.28, 4.25)
	≥ 300	4.53 (2.12, 9.66)	4.27 (1.96, 9.26)	3.28 (1.40, 7.66)
	p for the trend	<0.001	<0.001	0.001

PAD = Peripheral arterial disease; ACR = albumin to creatinine ratio.

^a Adjusted by sex, age.

^b Adjusted by sex, age, BMI, smoking, diabetic duration, systolic BP, HDL, LDL, triglyceride, fasting blood glucose, and HbA_{1c}.

^c Carotid plaque was dichotomized according to the number of plaques (≤ 1 or >1).

^d PAD was dichotomized according to ABI ≤ 0.9 or ABI >0.9 .

likely to be hypertensive, have more plaque in their carotid arteries, and have a higher percentage of their ABIs ≤ 0.9 .

ORs for Carotid Plaque and PAD according to ACR Level

The ORs for carotid plaque and PAD according to ACR level are listed in table 2. When adjusted by sex and age, albuminuria was not significantly associated with carotid plaque, but was significantly associated with PAD (OR 2.57; 95% confidence interval (CI) 1.46–4.52 for normoalbuminuria vs. microalbuminuria and OR 4.27; 95% CI 1.96–9.26 for normoalbuminuria vs. macroalbuminuria). When additionally adjusted for other covariates (i.e. BMI, smoking, diabetic duration, systolic BP, HDL, LDL, triglyceride, fasting blood glucose, and HbA_{1c}), albuminuria was not significantly associated with plaque; however, the significant association between albuminuria and PAD was slightly attenuated (OR 2.33; 95% CI 1.28–4.25 for normoalbuminuria vs. microalbuminuria and OR 3.28; 95% CI 1.40–7.66 for normoalbuminuria vs. macroalbuminuria).

Comparison between IMT and baPWV Means according to ACR Level

The means and standard errors for CCA-IMT and baPWV according to ACR level are listed in table 3. The mean CCA-IMT value was not significantly different according to ACR level (0.73, 0.74, 0.72, and $p = 0.399$); however, a significant difference was found in the mean

baPWV value according to ACR level after adjusting for other covariates (1,764.79, 1,778.98, 2,001.33, and $p < 0.001$).

Discussion

We evaluated the association between albuminuria, carotid atherosclerosis, arterial stiffness, and PAD in Korean type 2 diabetics. We found that ACR level was strongly associated with PAD and baPWV, when adjusted for other CVD risk factors, such as gender, age, BMI, smoking, diabetic duration, systolic BP, HDL, LDL, triglyceride, fasting blood glucose, and HbA_{1c}. No significant association, however, was observed between ACR levels, carotid plaque, and CCA-IMT.

In this study, after adjusting for other covariates, ACR levels were not significantly associated with carotid plaque (OR 1.36; 95% CI 0.72–2.55 for normoalbuminuria and macroalbuminuria) or the mean CCA-IMT value (0.73, 0.74, and 0.72; $p = 0.399$). In a cross-sectional study of 368 participants [17], researchers divided the participants into two groups according to urine albumin excretion (UAE): normoalbuminuria (UAE $<20 \mu\text{g}/\text{min}$) and microalbuminuria (UAE 20–200 $\mu\text{g}/\text{mg}$). When they compared the number of carotid plaques, no significant difference was found between subjects with normoalbuminuria and microalbuminuria. In another study of 830 subjects, Ishizaka et al. [22] reported that albuminuria was positively associated with carotid IMT (OR 2.21;

Table 3. Comparison between IMT and baPWV means according to ACR level

	ACR μg/mg creatinine	Non-adjusted mean (SE)	Model 1 ^a mean (SE)	Model 2 ^b mean (SE)
CCA-IMT	<30	0.73 (0.01)	0.73 (0.01)	0.73 (0.01)
	30–299	0.75 (0.01)	0.75 (0.01)	0.74 (0.01)
	≥300	0.73 (0.02)	0.73 (0.02)	0.72 (0.02)
	p	0.162	0.333	0.399
baPWV ^c	<30	1,726.83 (21.81)	1,727.52 (19.80)	1,764.79 (18.53)
	30–299	1,819.73 (26.40)	1,817.48 (23.99)	1,778.98 (22.41)
	≥300	2,089.63 (59.03)	2,095.85 (53.58)	2,001.33 (49.92)
	p	<0.001	<0.001	<0.001

CCA = Common carotid artery; IMT = intima-media thickness; baPWV = brachial-ankle pulse wave velocity.

^a Adjusted by sex, age.

^b Adjusted by sex, age, BMI, smoking, diabetic duration, systolic BP, HDL, LDL, triglyceride, fasting blood glucose, and HbA_{1c}.

^c Calculated with the patients with their ABI ≥0.9 after excluding the patients with ABI <0.9.

95% CI 1.15–4.23); however, this association disappeared after adjusting for age (OR 1.26; 95% CI 0.61–2.61). Similar results have been published for diabetic patients. Consistent with our results, in a study of 588 type 2 diabetic patients, investigators estimated the association between log(ACR) and carotid IMT, but log(ACR) was not associated with carotid IMT ($p = 0.1194$) [23].

Based on our results, albuminuria was not associated with carotid plaque or IMT. There may be several explanations for this. First, the diabetic state itself has such a powerful influence on carotid plaque and CCA-IMT that any effect of albuminuria is masked. In diabetics, it has been suggested that the endothelium is stressed by advanced glycosylation end products, leading to increased albumin permeability [24], and that disturbed proteoglycan synthesis causes the glomerular membrane to lose its charge sensitivity and integrity [25]. Second, because carotid plaque formation and progression commonly occur at places of non-laminar turbulent flow, such as the proximal internal carotid artery or at the bifurcation [26], measures of CCA-IMT might not be representative of what is actually occurring at more atherosclerosis-prone locations [27].

We found that mean baPWV values were significantly different according to ACR level after adjusting for potentially confounding variables (1,764.79, 1,778.98, and 2,001.33, respectively; $p < 0.001$). In a study of 346 type 2 diabetic patients [15], researchers investigated the association between baPWV and ACR. They categorized patients into three groups, according to ACR level: normo-

albuminuria (<30 μg/mg creatinine), microalbuminuria (30–299 μg/mg creatinine), and macroalbuminuria (≥300 μg/mg creatinine). They found that baPWV was significantly higher in patients with macroalbuminuria or microalbuminuria, compared with normoalbuminuria patients. Additionally, ACR was significantly associated with baPWV ($r = 0.24$; $p < 0.0001$) and was an independent risk factor for baPWV. In a study of 167 type 2 diabetic patients, Ishimura et al. [28] reported that aortic PWV was significantly correlated with log(UAE) ($r = 0.269$; $p < 0.0001$). In a multiple regression analysis, log(UAE) was an independent risk factor for aortic PWV after adjustment for other CV factors ($R^2 = 0.246$; $p < 0.0001$).

Arterial stiffness is a major contributor to CVD [29] and aortic PWV is one of a few indices of arterial stiffness that has been directly linked with cardiovascular mortality and morbidity [30]. However, baPWV is still a relatively new measure of arterial stiffness [31], compared with aortic PWV, and they are differentiated in that baPWV reflects a combination of aortic and peripheral stiffness [32]. Nevertheless, at both clinical and subclinical levels, baPWV correlates with the degree of atherosclerotic vascular damage [33], similar to aortic PWV.

A possible explanation for the mechanism linking arterial stiffness and albuminuria is that increased arterial stiffness is a major cause of a wide pulse pressure and systolic hypertension [34]. An increase in arterial pulse pressure could contribute to glomerular damage, because kidney cells have no protection against pulsatile stress [35].

Hypertension has been significantly associated with microalbuminuria [36], because systemic BP affects the loss of albumin from the renal glomerulus. However, in a study of 136 community residents [37], after adjusting for other covariates, including systolic BP and pulse pressure, microalbuminuria was independently associated with PWV, indicating that the association was not merely a reflection of the increases in pulse pressure and systolic BP.

Similar to our results, several studies have shown an association between ACR and PAD (OR 2.33; 95% CI 1.28–4.25 for normoalbuminuria vs. microalbuminuria and OR 3.28; 95% CI 1.40–7.66 for normoalbuminuria vs. macroalbuminuria). For example, in a cross-sectional study of 3,312 subjects, researchers investigated the ORs of subclinical CVD with and without microalbuminuria [38]. In their analysis of type 2 diabetic patients, microalbuminuria was significantly associated with ABI, after adjustment for other covariates (OR 6.05; 95% CI 1.61–22.76). In another study with 290 type 2 diabetic patients, Tseng et al. [39] found that patients with PAD had a significantly higher $\ln(\text{ACR})$ value than those without PAD, and $\ln(\text{ACR})$ was correlated with ABI ($r = -0.198$; $p < 0.01$). After adjustment for other CV risk factors, albuminuria was significantly associated with PAD (OR 2.54; 95% CI 1.05–6.17 for normoalbuminuria vs. microalbuminuria and OR 5.86; 95% CI 1.76–19.52 for normoalbuminuria vs. macroalbuminuria).

In our study, albuminuria was associated with PAD, but not carotid plaque or CCA-IMT. We presently have no explanation for this difference between the three vessel structure markers. A possible explanation is that although they are similar, they are not identical factors [40]. Peripheral artery plaques are relatively more stable and less likely to rupture [40] and PAD may have a microvascular component [41] and shared pathogenesis with retinopathy [42].

One possible explanation for the association between atherosclerosis and albuminuria is that vascular endothelial damage can cause atherosclerosis and albuminuria [43]. Endothelial dysfunction changes the endothelial properties and has structural and functional effects on the target vessel, including changes in hemostasis and fibrinolysis, vasomotor activity, permeability to macromolecules, leukocyte adhesion, and vascular smooth muscle cell proliferation [44]. Thus, endothelial dysfunction plays a key role in the initiation and progression of atherosclerosis [44]. Additionally, endothelial dysfunction affecting the glomerular basement membrane could modify glomerular barrier permeability, leading to albumin excretion into the urine [45].

Lipid profiles may also affect the association between IMT, carotid plaque, and albuminuria. Glomerular cells possess LDL receptors, and mesangial and glomerular epithelial cells can internalize atherogenic lipoproteins via receptor-mediated and non-receptor-mediated mechanisms [46]. The infiltration of atherogenic lipoproteins into the glomerular endothelium and mesangial cells can trigger a series of events, such as adhesion molecule expression, monocyte chemoattractant production, and the release of reactive oxygen species, which lead to glomerular injury [47]. Thus, we suggest that lipid profiles, such as LDL cholesterol, might confound the association between atherosclerosis and albuminuria. In the present study, examination of the crude OR and sex-age-adjusted OR showed that albuminuria was marginally associated with carotid plaque; however, this association disappeared when additionally adjusted for other covariates. When we assessed the effects of other covariates, respectively, LDL cholesterol exerted a major influence on this disassociation.

This study possesses several limitations. First, we did not observe the incidence of CVD and PAD events, but, instead, attempted to predict the incidence of CVD and PAD, based on such indicators as IMT, carotid plaque, baPWV, and ABI, known surrogates for atherosclerosis and PAD. Second, we used a single morning spot urine sample to assess microalbuminuria, instead of timed urine collections, which would have been preferable. However, early morning urine provides a good estimate of 24-hour urinary albumin excretion rates, and a urinary ACR >3.0 mg/mmol is associated with an albumin excretion rate >30 mg/min, with high sensitivity and specificity [48]. Despite its limitations, this study is valuable in that we evaluated the association between various subclinical atherosclerosis phenotypes, such as CCA-IMT, carotid plaque, ABI, and baPWV, in a single population.

In conclusion, albuminuria was significantly associated with baPWV and PAD, but not carotid plaque or CCA-IMT in Korean type 2 diabetic patients. Additional prospective studies are required to further evaluate the mechanisms underlying these associations, and lack of associations, in Korean patients with type 2 diabetes.

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