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Albuminuria and peripheral arterial disease: Results from the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background: The association of albuminuria with cardiovascular disease (CVD) is increasingly recognized, but its association with peripheral arterial disease (PAD) is not well characterized in subjects with or without diabetes.

Methods: Using data from the Multi-Ethnic Study of Atherosclerosis, a cohort free of clinical vascular disease, we analyzed the cross-sectional association between albuminuria and PAD in diabetic and nondiabetic subjects. A spot urine albumin-creatinine ratio (ACR) was used to define albuminuria in two ways: presence or absence of albuminuria and the degree of albuminuria (no albuminuria defined as urine ACR < 17 mg/g for men and < 25 mg/g for women, microalbuminuria as urine ACR 17 to 249 mg/g for men and 25 to 334 mg/g for women, and macroalbuminuria as urine ACR ≥ 250 mg/g for men and ≥ 355 mg/g for women). PAD was defined by ankle-brachial index (ABI) < 0.9.

Results: Among the 6,760 subjects, aged 45-84 years, 326 (4.8%) had prevalent PAD. 813 (12.0%) subjects had microalbuminuria and 100 (1.5%) had macroalbuminuria. Among diabetic subjects, those with albuminuria (micro and macroalbuminuria combined) were 1.90 times more likely to have PAD (95% CI: 1.19-3.04) than those with no albuminuria. After adjusting for CVD risk factors, the odds ratio modestly attenuated to 1.65 (95% CI: 1.00-2.74). For nondiabetic subjects, there were no statistically significant associations observed in the univariable and multivariable analyses. The degree of albuminuria was not associated with PAD in either diabetic or nondiabetic subjects.

Conclusions: The presence, but not magnitude of albuminuria, is an important risk factor for PAD in diabetic but not in nondiabetic subjects.

Keywords

Albuminuria; Peripheral arterial disease; Epidemiology; Risk factors

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1. Introduction

It is increasingly recognized that albuminuria is not only a marker of kidney damage, but is also associated with increased risk of cardiovascular morbidity and mortality. This evidence is derived from investigations of the general population [1,2], as well as high-risk populations, including patients with diabetes [3] and those with known hypertension and left ventricular hypertrophy [4]. For example, in the Heart Outcomes Prevention Evaluation Study, diabetic subjects with microalbuminuria, defined by urine albumin/creatinine ratio (ACR) > 2, had an almost two-fold increased risk of first major cardiovascular disease (CVD) events compared to those with no microalbuminuria [5]. Albuminuria has been shown to be independently associated with several measures of subclinical CVD, including left ventricular mass [6] and higher carotid intima-medial thickness in both diabetic and nondiabetic subjects [7]. These findings support the potential pathophysiologic relationship between albuminuria and generalized early atherosclerotic disease. If true, albuminuria might also be related to atherosclerotic peripheral arterial disease (PAD) of the lower extremities.

Most epidemiologic studies have shown an increased risk of PAD in patients with chronic kidney disease [8,9]. However, the role of albuminuria as a risk factor for PAD has been evaluated in mostly small studies. These studies suggest that albuminuria may be an important risk factor for PAD in the general population [10,11] and in high risk populations of diabetic subjects [12-15] or hypertensive subjects [16,17]. The hypothesis of this study was that albuminuria is associated positively with PAD in a racially diverse group of diabetic and nondiabetic subjects without a history of CVD.

2. Research design and methods

2.1. Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based investigation of the prevalence, correlates, and progression of subclinical CVD. Detailed descriptions of the MESA study design and objectives have been previously published [18]. Briefly, the study cohort comprised 6814 men and women aged 45 to 85 years, recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County; NC; Los Angeles County, CA; northern Manhattan, NY, and St. Paul, MN) between July 2000 and August 2002. Subjects enrolled in MESA were free of clinical CVD at baseline and included 38% Whites, 28% African Americans, 23% Hispanics, and 11% Asians (of Chinese descent), and approximately 50% females. Institutional review board approval was obtained at all MESA sites.

2.2. Measurement of baseline risk factors

After informed consent, the MESA subjects completed self-administered questionnaires, underwent examinations by trained research staff, and provided fasting blood and urine samples. Subjects were classified as never, former, or current smokers. Body mass index (BMI) was calculated as measured weight in kilograms divided by the square of measured height in meters. Systolic blood pressure was measured three times in the seated position with a Dinamap model PRO 100 automated oscillometric sphygmomanometer (Critikon, Inc., Tampa, FL), and the average of the final two systolic blood pressure measurements was used for the study. Prevalent diabetes was defined as fasting serum glucose level ≥ 7.0 mmol/L (126 mg/dL) or current use of any diabetes medication. Subjects were asked to bring all current medications used to the study visit.

Fasting blood samples were drawn under standardized conditions. High density lipoprotein (HDL) cholesterol was measured using the cholesterol oxidase method (Roche Diagnostics) and low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.

2.3. Urine albumin and creatinine ratio

A spot urine sample was collected. Urine albumin and creatinine were measured using nephelometry and the Jaffe method, respectively. Urine albumin-creatinine ratio (ACR) was calculated and was categorized as follows: 1) no albuminuria (urine ACR < 17 mg/g for men and < 25 mg/g for women); 2) microalbuminuria (urine ACR between 17 to 249 mg/g for men and 25 to 349 mg/g for women); and 3) macroalbuminuria (urine ACR ≥ 250 mg/g for men and ≥ 355 mg/g for women) [19]. Albuminuria for this analysis was defined as presence of either microalbuminuria or macroalbuminuria.

2.4. Measurement of ankle-brachial index

Blood pressure measurements for calculation of the ankle brachial index (ABI) were obtained using a 5-mHz Doppler probe (Nicolet Vascular, Golden, CO) on bilateral brachial, posterior tibial, and dorsalis pedis arteries. Brachial artery pressure was obtained by averaging the left and right brachial blood pressures. If the two brachial blood pressures differed by 10 mmHg or more, the higher brachial blood pressure was used as the ABI denominator. The maximum right and left ankle blood pressures were obtained by taking the highest posterior tibial or dorsalis pedis arteries blood pressure from each leg. The ABI was calculated as a ratio of the maximum of ankle blood pressure divided by the average of brachial blood pressure. The lower of the right or left leg ABI was used for the analyses. In this study, PAD was defined by ABI < 0.9. Because a recent study has demonstrated that subjects with ABI > 1.4 have an increase CVD mortality similar to those with ABI < 0.9 [20], PAD was also defined as ABI < 0.9 or > 1.4.

2.5. Statistical analysis

Of the eligible sample of 6,814 subjects, we excluded 39 subjects with missing data on □albuminuria, leaving 6,760 subjects for the analysis. For descriptive purposes, the means and proportions of demographic and clinical variables were compared in subjects with or without PAD (ABI < 0.9), with adjustment for age, sex, race, and center, using an analysis of covariance. Urine ACR was modeled dichotomously (presence or absence of □albuminuria). With no □albuminuria as the reference group, logistic regression was used to calculate odds ratios and 95% confidence intervals of PAD. Model 1 was adjusted for demographic factors, including age, race, sex, and MESA field center. Model 2 was additionally adjusted for cigarette smoking status, pack years of smoking, LDL and HDL cholesterol, systolic blood pressure, BMI, and use of antihypertensive medications. These covariates were modeled as continuous variables, except for smoking status (never, former, and current smokers) and use of antihypertensive medication (yes, no). In the supplementary analysis, the same analysis was performed in which PAD was defined as ABI < 0.9 or > 1.4. All statistical analyses were conducted using SAS software version 8.2 (SAS Institute, Cary, NC).

3. Results

Among the 6,760 MESA subjects without clinical CVD, aged 45-84 years, 326 (4.8%) had prevalent PAD (ABI < 0.9) and 42 (0.6%) had ABI > 1.4. The mean ABI among PAD subjects was 0.8. The majority of PAD cases were African American (44.2%) or Caucasian (35.0%), whereas Hispanics and Asians together accounted for only 20.8%. As expected, those with PAD had a worse risk factor profile. Compared with subjects without PAD, those who had PAD were more likely to be older and male and have higher prevalences of hypertension, diabetes, and current smoking as well as greater mean values for pack-years of cigarette use, systolic blood pressure, and serum creatinine and a lower mean HDL cholesterol level (Table 1).

Table 2 presents the association of albuminuria with PAD in subjects with or without diabetes. After adjustment for demographic factors, among diabetics, compared to those with no albuminuria, those with albuminuria were 1.90 times more likely to have PAD (95% CI: 1.19-3.04) (Model 1). After further adjustment for major CVD risk factors, the odds ratio modestly attenuated to 1.65 (95% CI: 1.00-2.74) (Model 2). For nondiabetic subjects, Model 1 was suggestive of an increased risk, with an odds ratio of 1.44 (95% CI: 0.99-2.05), but Model 2 indicated the excess risk was largely due to confounding by major CVD risk factors.

There were 813 subjects (12.0%) with microalbuminuria and 100 (1.5%) with macroalbuminuria. The degree of albuminuria was not associated with PAD in either diabetic or nondiabetic subjects. This is likely due to the small number of PAD cases in both groups. For the diabetic group, the multivariable adjusted odds ratio comparing to subjects with no albuminuria was 1.70 (95% CI: 0.99-2.89) for those with microalbuminuria (n=33 PAD cases) and 2.19 (95% CI: 0.91-4.97) for those with macroalbuminuria (n=10 PAD cases). For the nondiabetic group, the analogous odds ratio was 1.14 (95% CI: 0.75-1.68) for microalbuminuria (n= 38 PAD cases) and 1.49 (95% CI: 0.34-4.55) for macroalbuminuria (n=3 PAD cases).

3.1. Supplemental analysis

A recent study has demonstrated that subjects with ABI > 1.4 have an increase in ischemic leg pain and an increase in CVD mortality similar to those with ABI < 0.9 [21]. We therefore redefined PAD as ABI < 0.9 or > 1.4 (n=368 PAD cases) and repeated the same analysis. The multivariable adjusted odds ratio of PAD with albuminuria was 1.47 (95% CI: 0.91-2.39) for diabetic subjects (n=100 PAD cases) and 1.24 (95% CI: 0.85-1.76) for nondiabetic subjects (n=268 PAD cases). No statistically significant associations were noted when stratified by the degree of albuminuria in subjects with or without diabetes (data not shown).

4. Discussion

The main finding of this population-based study is that the presence of albuminuria was associated with an almost 2-fold greater prevalence odds of PAD in diabetic subjects. This magnitude of association is comparable to that of known PAD risk factors such as hypertension, hyperlipidemia, and diabetes [22]. On the other hand, there was no association of albuminuria and PAD among nondiabetic subjects. The data were suggestive of a dose-response association between the amount of albuminuria and PAD, but the results were not statistically significant. This is likely due to the small number of PAD cases in the microalbuminuria and macroalbuminuria groups.

A number of cross-sectional studies have consistently reported that albuminuria is independently associated with subclinical and clinical manifestations of PAD in the diabetic population. The Cardiovascular Heart Study found that albuminuric diabetic subjects with or without hypertension were six times more likely to have PAD (ABI < 0.9) than their counterparts without albuminuria [1]. Albuminuria has also been associated with an increased incidence of lower extremity amputation (n=1056) in type 2 diabetic subjects [15], and in another study the greater the amount of albuminuria, the higher the prevalence of foot ulcers (n=557) in type 2 diabetes [14]. Our findings are compatible with those of prior studies and provide additional evidence supporting the hypothesis that the presence of albuminuria is a risk factor for generalized vascular damage. On the other hand, albuminuria may be just a marker of longer duration or more severe diabetes and not the true cause of diabetes-related vascular damage [23].

For the nondiabetic population, evidence of an association between albuminuria and PAD is conflicting. Using the nondiabetic subset data from the Islington Diabetes Survey (n=187),

Yudkin et al has shown that the prevalence of PAD (ABI < 0.9) increased sixfold in subjects with microalbuminuria (urinary albumin excretion rate 20-200 μg/min) compared with those with no albuminuria [24]. In a later cross-sectional analysis with a larger sample size (n=913), this association was observed only in women: women in the top quartile of urinary albumin excretion rate (≥ 5.07 μg/min) had an almost fourfold greater prevalence of PAD compared with women in the lowest quartile (< 1.65 μg/min) [25]. In contrast, our study found at best a modest association in nondiabetic subjects. In line with our findings, the Cardiovascular Heart Study [11] also reported no associations of albuminuria with other subclinical markers of cardiovascular disease (carotid artery intima-media thickness and left ventricular mass) in nondiabetic subjects. That study, however, was not able to evaluate the albuminuria-ABI association due to its small sample size of subjects with no diabetes or hypertension. Taken together, findings from the MESA and the Cardiovascular Heart Study, two large population-based studies, suggest that albuminuria is not an independent risk factor for PAD in the low risk population without diabetes or hypertension.

Although not well understood, there are several pathophysiologic mechanisms that might explain the association between albuminuria and PAD. In several studies, albuminuria is associated with a number of well-established CVD risk factors. These include smoking, diabetes, hyperlipidemia, hypertension, and inflammatory markers [26,27], most of which are known risk factors for PAD [28]. Furthermore, it has been suggested that albuminuria may be a marker of endothelial dysfunction [29]. In diabetic subjects, hyperglycemia induces endothelial cells to generate excessive reactive oxygen species and advanced glycation end products [30]. These products, in turn, bind to specific receptors on endothelial cells and activate transcription of injurious cytokines and chemokines, resulting in vascular endothelial cell damage. These processes can lead to initiation of local thrombotic events at the site of endothelial injury and platelet activation and aggregation. The increased platelet activity may also stimulate proliferation of vascular smooth muscle cells, which is believed to play a major role in the development and progression of lower extremity atherosclerosis, and consequently clinical PAD.

The strengths of this study include a large sample size of several race/ethnicity groups, and the rigorous methodology used in MESA. We also acknowledge a series of limitations. First, the cross-sectional nature limits conclusions about causality and directionality of the association observed in this study. Second, this study had only a single measurement of albuminuria. Even in the absence of chronic kidney disease, albuminuria can increase transiently in a number of other medical conditions such as exercise or fever. This misclassification would bias the observed results toward the null.

We conclude from this community-derived population that albuminuria is a more important risk factor for PAD in diabetic subjects than in nondiabetic subjects. This finding needs to be confirmed in a prospective study, which could help elucidate the direction of association. If confirmed, albuminuria may be clinically useful in identifying diabetic subjects at risk for PAD.

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Table 1

Mean or prevalence of risk factors according to prevalent peripheral arterial disease (PAD)[a] status: the Multi-Ethnic Study of Atherosclerosis (MESA)

Baseline Risk Factor	Prevalent PAD		p-value
	Yes (n=326)	No (n=6,449)	
Age (yr)	70	62	<0.0001
Male, %	41	48	0.01
Race/ethnicity, %			
White, %	35.0	38.7	0.20
Black, %	44.2	26.9	
Chinese, %	5.8	12.2	
Hispanic, %	15.0	22.3	
Hypertension, %[b]	55.2	44.3	<0.0001
Use of antihypertensive medications, %[b]	47.5	36.7	<0.0001
Diabetes, %[b]	24.7	13.7	<0.0001
Current smoking, %[b]	24.7	12.9	<0.0001
Total cholesterol, mg/dl[b]	196	194	0.44
LDL cholesterol, mg/dl[b]	119	117	0.22
HDL cholesterol, mg/dl[b]	49	51	0.004
Pack years of cigarette use[b]	19.7	11.0	<0.0001
Systolic blood pressure[b]	131	126	0.0002
Body mass index, kg/m^2[b]	28.2	28.3	0.64
Serum creatinine, mg/dl[b]	1.0	0.9	<0.0001
Ankle-brachial index[b]	0.78	1.13	<0.0001

[a] PAD is defined as ankle brachial index < 0.9

[b] Adjusted for age, sex, race, and MESA field center

Table 2

Odds ratios and 95% confidence intervals of peripheral arterial disease (PAD)[a] according to the presence or absence of albuminuria, the Multi-Ethnic Study of Atherosclerosis (MESA)

	Albuminuria absent	Albuminuria present
Diabetic subjects (n=965)	630	335
PAD cases (n=90)	47	43
Model 1[b]	1.0	1.90 (1.19-3.04)
Model 2[c]	1.0	1.65 (1.00-2.74)
Nondiabetic subjects (n=5795)	5217	578
PAD cases (n=236)	195	41
Model 1[b]	1.0	1.44 (0.99-2.05)
Model 2[c]	1.0	1.13 (0.76-1.65)

[a] PAD is defined as ankle brachial index < 0.9

[b] Model 1 adjusted for age, sex, race, and center

[c] Model 2 adjusted for covariates in Model 1 plus cigarette smoking, pack years of smoking, LDL and HDL cholesterol, systolic blood pressure, body mass index, and use of antihypertensive medication