Low-grade albuminuria is associated with peripheral artery disease in Chinese diabetic patients

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A B S T R A C T

Background: Increasing studies have suggested that albuminuria might be an important risk factor for peripheral artery disease (PAD). However, studies focusing on the association between low-grade albuminuria and PAD are limited. It would be of great interest to elucidate the association between low-grade albuminuria and PAD in diabetic subjects.

Methods: A cross-sectional study was conducted in 1386 diabetic subjects (age ≥ 40 years) with normal urinary albumin levels from Shanghai, China. A first voided early morning spot urine sample was obtained for urinary albumin and creatinine measurements. Subjects were divided into three groups according to sex-specific cutoff points of urinary albumin–creatinine ratio (UACR) tertiles. Subjects in the upper tertile of UACR were classified as having low-grade albuminuria. PAD was defined by ankle–brachial index (ABI) < 0.9 or > 1.4.

Results: Overall, 106 (7.7%) of the study population had PAD. The prevalence of PAD in tertile 3 of UACR was higher than the prevalence in tertile 2 and tertile 1 (10.2%, 6.4% and 6.4%, respectively; P < 0.05). A fully adjusted logistic regression analysis revealed that compared with subjects in tertile 1 of normal UACR, those in tertile 3 had 1.7-fold increased risk for the presence of PAD.

Conclusions: In diabetic patients, high normal UACR level, which is below the current cutoff point of microalbuminuria, was associated with the increased prevalence of PAD. It suggested that low-grade albuminuria might be an early marker for the detection of PAD in diabetic patients.

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1. Introduction

Microalbuminuria was first reported in diabetic patients by Viberti in 1982 [1]. It has been shown to be associated with increased risk of cardiovascular morbidity and mortality. This evidence was derived from investigations in the general population [2, 3], as well as in high-risk populations, including patients with diabetes [4] and/or hypertension [5]. Recently, albuminuria below cutoff point was also revealed to be associated with cardiovascular morbidity and mortality [6, 7]. The Heart Outcomes Prevention Evaluation (HOPE) Study [6] indicated that any degree of albuminuria was a risk factor for cardiovascular events in individuals with or without diabetes and the risk increased with the urinary albumin–creatinine ratio (UACR), starting well below the microalbuminuria cutoff point.

Peripheral artery disease (PAD) is a manifestation of generalized atherosclerosis. Patients with PAD tend to develop ulceration, pain, claudication, necrosis and amputation of the lower extremities, which may lead to disability among diabetic and elderly persons. Studies have also demonstrated that patients with PAD were at higher risks of cardiovascular morbidity and mortality [8–10].

Epidemiologic studies [3, 11, 12] have suggested that macro- and microalbuminuria might be an important risk factor of PAD. However, studies evaluating the possible association between UACR below cutoff point of microalbuminuria and PAD are limited. It would be of great interest to elucidate the association between low-grade albuminuria and PAD in diabetic patients.
2. Research design and methods

2.1. Population

A cross-sectional study with a cluster sampling design was conducted in Jiading District, Shanghai China from March to August, 2010. During the recruiting phase, a total of 10,569 subjects who aged 40 years or above were invited to participate by advertisement and home visits. Totally, 10,375 subjects signed the consent form and agreed to take part in the survey, with a participation rate of 98.2%. The study design and data collection were described previously [13]. Among those participants, 1872 subjects with fasting plasma glucose (FPG) ≥7.0 mmol/L and/or 2 h plasma glucose (2h-PG) ≥11.1 mmol/L or with a history of diabetes were included in the study. The diagnosis of diabetes was defined according to the 1999 World Health Organization criteria [14]. Subjects who met the following criteria were excluded sequentially from the analyses: 1) 5 subjects without urine samples, 2) 53 subjects without ankle–brachial index (ABI) measurement, 3) 10 subjects with estimate glomerular filtration rate (eGFR) <60 ml/min/1.73 m², 11 subjects with glomerulonephritis, nephritic syndrome or malignancy, 4) 222 subjects with macroalbuminuria or microalbuminuria (5) and 185 subjects with clinical cardiovascular diseases, a total of 1386 subjects were included in the analysis. This study was conducted with the approval of the Institutional Review Board of Ruijin Hospital affiliated to Shanghai Jiao-Tong University School of Medicine. All participants provided informed consent.

2.2. Diagnosis of PAD

ABI, an indicator of PAD, defined as the ratio of systolic blood pressure of the ankle to that of the arm, was measured by a fully automatic arteriosclerosis diagnosis device (Colin VP-1000, Model BP203RPE II, form PWV/ABI) with subjects in the supine position, after resting for 10–15 min. Ankle and brachial arterial pressures were detected at the same time and ABI was calculated automatically for both sides. Subjects who had an ABI <0.9 or >1.4 at either side, were diagnosed as having PAD [15].

2.3. Urine albumin and creatinine ratio

A first morning spot urine sample was obtained at the survey center. Urine albumin and creatinine were measured by immunoturbidimetric method (Beijing Atom High-Tech, Beijing, China) and the Jaffe’s kinetic method on an automatic analyzer (Hitachi 7600-020, Tokyo, Japan) respectively. The UACR in mg/g was calculated as urine albumin concentration divided by urine creatinine concentration. The study population was divided into tertiles on the basis of urine albumin concentration divided by urine creatinine concentration. The study population was divided into tertiles on the basis of the cation of diet in renal disease (MDRD) formula that validated for Chinese patients: eGFR = [186 × serum creatinine (mmol/L)] × 0.1133 × age^{−0.203} × (0.742 for women) × 1.233 [17].

2.5. Statistical analysis

Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Continuous variables in normal distribution were presented as means ± SD, while skewed variables were presented as medians (interquartile range) and logarithmically transformed before analysis. Trends in means and proportions were tested using linear regression and χ² tests, respectively. Univariate and multivariate logistic regression were used to evaluate the association between UACR and PAD. Variables in multivariate regression model included age, sex, BMI, smoking status, drinking status, leisure-time physical activity, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), HOMA-IR, low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), total cholesterol (TC), triglycerides (TG), eGFR, anti-diabetic treatment and diabetes duration. Two-sided P values <0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study population

Overall, 106 (7.7%) of the study population had PAD. Across the UACR tertiles, the prevalence of PAD was 6.4%, 6.4% and 10.2%, respectively (P for trend = 0.04). Patients were divided into three groups according to sex-specific cutoff points of UACR tertiles. General characteristics of the study population by UACR tertiles were summarized in Table 1. Age, SBP, FPG, HbA1c, HOMA-IR, TG, eGFR and the prevalence of low ABI (ABI < 0.9) increased significantly with elevated UACR levels (all P for trend < 0.05). However, gender distribution, BMI, DBP, TC, HDL-c, LDL-c and diabetes duration were not statistically different among the three groups; likewise, the prevalence of anti-diabetic treatment, current smoking, current drinking, high leisure-time physical activity and high ABI (ABI > 1.4) also showed no statistical differences across UACR tertiles.

3.2. Association between low-grade albuminuria and PAD

In the univariate model, participants in the highest tertile were at significantly increased risk for the presence of PAD compared with participants in the lowest tertile (OR = 1.7, 95% CI: 1.0–2.7, P = 0.04). In the multivariate model, participants in the highest tertile remained at being 1.7 times more likely to have PAD compared with those in the lowest tertile (OR = 1.7; 95% CI: 1.0–2.8, P = 0.04; Table 2).
4. Discussion

In the present study, we found that in diabetic patients with normal albumin levels in urine (UACR < 30 mg/g), low-grade albuminuria was associated with the presence of PAD, which has been demonstrated to be linked with higher risks of cardiovascular morbidity and mortality. Moreover, the association of low-grade albuminuria with PAD was independent of other traditional cardiovascular risk factors [19,20]. Apart from the associations between albuminuria and several conventional cardiovascular risk factors reported, significant correlations between increased UACR and nontraditional risk factors for cardiovascular diseases have been observed. Indeed, several cross-sectional investigations documented that albuminuria was related to various inflammatory markers [21-23]. It is well acknowledged that generalized endothelial dysfunction plays an important role in both initiation and progression of atherosclerosis. Albuminuria has repeatedly been shown to be accompanied by abnormalities in various markers of endothelial cell function in patients with and without diabetes. Increased plasma levels of some markers of endothelial damage and dysfunction have been observed in individuals with albuminuria [24,25]. Albuminuria has also been proved to be associated with factors that may themselves be causal or linked with causal processes. These include hyperglycemia, hypertension, and dyslipidemia [19,20]. Apart from the associations between albuminuria and various conventional cardiovascular risk factors reported, significant correlations between increased UACR and nontraditional risk factors for cardiovascular diseases have been observed. Indeed, several cross-sectional investigations documented that albuminuria was related to various inflammatory markers [21-23]. It is well acknowledged that generalized endothelial dysfunction plays an important role in both initiation and progression of atherosclerosis. Albuminuria has repeatedly been shown to be accompanied by abnormalities in various markers of endothelial cell function in patients with and without diabetes. Increased plasma levels of some markers of endothelial damage and dysfunction have been observed in individuals with albuminuria [24,25]. Albuminuria has also been proved to be associated with factors that may themselves be causal or linked with causal processes. These include hyperglycemia, hypertension, and dyslipidemia [19,20].

4. Discussion

In the present study, we found that in diabetic patients with normal albumin levels in urine (UACR < 30 mg/g), low-grade albuminuria was associated with the presence of PAD, which has been demonstrated to be linked with higher risks of cardiovascular morbidity and mortality. Moreover, the association of low-grade albuminuria with PAD was independent of other traditional cardiovascular risk factors.

Studies reported that microalbuminuria was a strong and independent risk factor for subclinical cardiovascular diseases such as PAD and clinical cardiovascular diseases. Recently, several studies have focused on the association between low-grade albuminuria and cardiovascular diseases. In a cross-sectional study, Huang and colleagues [7] found that low-grade albuminuria was associated with carotid intima-media thickness in diabetic subjects. In a community-based sample of nonhypertensive and nonobstructive individuals, low-grade albuminuria predicted the development of cardiovascular disease [18]. Moreover, the HOPE study indicated that there was no evident threshold of UACR for the risk of cardiovascular disease in a continuous manner. It demonstrated that every 0.01 mg/g increment in UACR conferred a 5.9% increase of major cardiovascular events [6]. The results presented here suggested that the relationship between albuminuria and cardiovascular disease was not restricted to the albuminuria range; low-grade albuminuria was also strongly and independently associated with risks for the presence of subclinical cardiovascular disease and clinical cardiovascular disease.

PAD, a manifestation of generalized atherosclerosis, is known to affect lower-extremity function and quality of life. Recently, several studies demonstrated that PAD was also associated with higher risks of cardiovascular morbidity and mortality. Hence, early detection and intervention of PAD are critical. The association between microalbuminuria and PAD has been well described [3,11]. However, studies about the association between low-grade albuminuria and PAD are limited. In the present study, we found that low-grade albuminuria was significantly associated with PAD which was defined as ABI > 1.4 or ABI < 0.9. Nevertheless, we find that if we excluded subjects with ABI > 1.4, the association between PAD and each 1-SD elevated UACR was not significant.

The potential pathophysiological mechanism linking low-grade albuminuria to PAD is not fully established. In fact, a very small concentration of albuminuria is unlikely to be a direct cause. Albuminuria is considered to associate with several traditional cardiovascular risk factors and nontraditional risk factors that may themselves be causal or linked with causal processes. These include hyperglycemia, hypertension, and dyslipidemia [19,20]. Apart from the associations between albuminuria and various conventional cardiovascular risk factors reported, significant correlations between increased UACR and nontraditional risk factors for cardiovascular diseases have been observed. Indeed, several cross-sectional investigations documented that albuminuria was related to various inflammatory markers [21-23]. It is well acknowledged that generalized endothelial dysfunction plays an important role in both initiation and progression of atherosclerosis. Albuminuria has repeatedly been shown to be accompanied by abnormalities in various markers of endothelial cell function in patients with and without diabetes. Increased plasma levels of some markers of endothelial damage and dysfunction have been observed in individuals with albuminuria [24,25]. Albuminuria has also been proved to be associated with factors that may themselves be causal or linked with causal processes. These include hyperglycemia, hypertension, and dyslipidemia [19,20].

Our study adds evidence to the association between low-grade albuminuria and PAD. However, several limitations require consideration. First, it’s a cross-sectional study, in which no causality could be suggested. Second, UACR levels were determined by a single measurement and may not be accurately representative of the status of subject. Third, the impact of other medical conditions on albuminuria was not assessed. Forth, the diagnosis of PAD was determined on the basis of ABI, rather than angiography, which is currently the gold standard for diagnosis. However, ABI measurement is a simple, noninvasive procedure that can be performed easily in the outpatient setting. Fifth, random errors in measurement of a risk factor will introduce downward bias of an estimated association to a disease or a disease marker. This phenomenon is called regression dilution bias. Dilution bias also exists in our study and weaken the association between low-grade albuminuria and PAD. But we can not correct the bias in our study. Sixth, Because we used cluster sampling design to recruit the general population aged 40 years or above in Shanghai China, our conclusion can not apply to other age groups or ethnicity groups.

The present study showed that low-grade albuminuria was associated with the prevalence of PAD in diabetic subjects. Thus, the study provided additional evidence to the hypothesis that risks of PAD began to increase at a relatively low UACR level, which may be helpful for early detection of PAD in diabetic patients. And
further prospective studies are needed to illustrate the precise relationship between low-grade albuminuria and incident of PAD.

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