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Albuminuria Is the Stronger Risk Factor for Peripheral Arterial Disease than eGFR Decline in a Type 2 Diabetic Taiwanese Population

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Key Words
Macroalbuminuria · Glomerular filtration rate · Peripheral arterial disease · Ankle-brachial index · Diabetes

Abstract
Background: Several studies have shown the identified risk factors for peripheral arterial disease in individuals with diabetes, but relatively little information has been provided regarding the risk factors for peripheral arterial disease especially in individuals with renal insufficiency and albuminuria. ***Aims:*** In our study, we attempted to determine whether peripheral arterial disease is related to the reduction of estimated glomerular filtration rate (eGFR) or albuminuria in type 2 diabetic patients if both were measured. ***Methods:*** We included 478 type 2 diabetic patients that were more than 50 years old in this study and determined their urine albumin to creatinine ratio and eGFR. The ankle-brachial index was measured. ***Results:*** We found a prevalence of peripheral arterial disease of 12 and 11.7% in the normoalbuminuria and >90 ml/min/1.73 m^2 eGFR group. Simple logistic regression analysis showed that both macroalbuminuria and eGFR <60 ml/min/1.73 m^2 were significantly associated with peripheral arterial disease individually, but most interestingly in the multiple logistic regression analysis, macroalbuminuria and age are independent factors for peripheral arterial disease with a p value of 0.012 ($\beta = 1.014$) and <0.001 ($\beta = 0.107$), respectively. ***Conclusion:*** In summary, our study indicates that macroalbuminuria is a stronger indicator for peripheral arterial disease than eGFR <60 ml/min/1.73 m^2 in a type 2 diabetic population older than 50 years of age.

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Introduction

Peripheral arterial disease is an atherosclerotic occlusive disease of the lower extremities that is more prevalent in diabetic patients. Tseng [1] reported a 10% prevalence in a type 2 diabetic Taiwanese population, and the Heart Disease and Stroke Statistics of the American Heart Association revealed a prevalence of 8–12 million people in the US population [2]. However, it is expected that these figures are greatly underestimated, given that more patients with peripheral occlusive disease are asymptomatic of intermittent claudication, which is the most common symptom in patients suffering from peripheral occlusive disease, especially in elderly women [3].

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Kidney disease is a major complication of diabetes that markedly increases the risk of cardiovascular disease (CVD) and mortality. Albuminuria, which is believed to reflect hemodynamic disturbances within the glomerulus, has long been identified as a major prognostic indicator in individuals with diabetes [4, 5]. Impaired glomerular filtration rate (GFR), a complementary sign of kidney damage, is also associated with increased risk [5, 6]. As a result, screening for kidney disease using urinary albumin and serological markers of kidney function has become a cornerstone of diabetes care and facilitation-targeted interventions to prevent CVD and kidney disease progression [7]. Albuminuria and impaired GFR may provide additive prognostic information regarding health outcomes in diabetes. However, the joint association of albuminuria and impaired GFR with peripheral arterial disease has not been defined in this setting because few studies have evaluated albuminuria and GFR simultaneously, and studies have reached different conclusions [6, 8]. Although some studies have found a relation between peripheral arterial disease and either the presence of a decreased estimated GFR (eGFR) or increased urinary albumin excretion, both were only present in most of the elderly diabetic population. In our study, we joined the two different staging systems of diabetic kidney disease and found that macroalbuminuria is a stronger predictor of peripheral arterial disease than the reduction of eGFR.

Materials and Methods

Patient Population

478 type 2 diabetic patients, that were more than 50 years old, with or without symptoms of intermittent claudication, cold sensation, numbness and pain of lower extremities, from the outpatient department of metabolism at Kaohsiung Medical University Hospital were included in this study. Only 378 patients completed the collection of spot urine albumin. Exclusion criteria were hospitalized patients and patients with acute illness, malignancies and previous operations of the hips and lower extremities. This study was approved by our institutional review board (KMUH-IRB-970303).

Measurement of Baseline Characteristics

The systolic and diastolic blood pressures, body height and weight were obtained from all subjects. The diagnosis of retinopathy was determined using a CR6-45NM nonmydriatic retinal camera (Canon Inc., Tokyo, Japan). Biochemical analyses using an automatic biochemistry analyzer (Beckman-Coulter Inc., Fullerton, Calif., USA) were performed for fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, creatinine, and high-sensitivity C-reactive protein after 8–12 h of overnight fasting. HbA1c was measured in whole blood using ion exchange high-performance liquid chromatography (Variant^{TM} II Turbo, Biorad, Calif., USA). The mean of at least 2–3 spot urine albumin was collected within a 3- to 6-month period. They were then measured by radioimmunoassay (DPC, Los Angeles, Calif., USA) after the exclusion of specimens collected from exercise within 24 h, infection, congestive heart failure, marked hyperglycemia or marked hypertension that may elevate urinary albumin excretion over baseline values. The albumin to creatinine ratio (ACR; in mg/g) was calculated as urine albumin concentration divided by urine creatinine concentration. The body mass index (BMI) was calculated as body weight divided by body height squared. The eGFR was calculated using the Modification of Diet in Renal Disease formula [GFR = 175 $\times$ serum creatinine$^{-1.154}$ $\times$ age$^{-0.203}$ $\times$ 0.742 (if female) $\times$ 1.212 (if black patient)] [9].

The study population was further divided into three groups based on the urine ACR: normoalbuminuria (<30 mg/g; n = 233), microalbuminuria (30–300 mg/g; n = 69) and macroalbuminuria (>300 mg/g, n = 76). The same study population was further divided into four groups based on eGFR: >90 ml/min/1.73 m^2 (n = 103), 60–90 ml/min/1.73 m^2 (n = 206), 30–60 ml/min/1.73 m^2 (n = 146), and <30 ml/min/1.73 m^2 (n = 23).

Ankle-Brachial Index

The ankle-brachial index (ABI) was measured by a noninvasive ABI analyzer once. The ABI is defined as the ratio of the systolic blood pressure of the ankle to the systolic blood pressure of the arm. Patients are placed in a supine position, the systolic blood pressure is then measured in both arms, and the higher value is used as the denominator of the ABI. Then the systolic blood pressure is measured in both the dorsalis pedis and posterior tibial arteries by placing the cuff just above the ankle, and the higher value is the numerator of the ABI for each limb. Diagnostic criteria for peripheral arterial disease are considered to be an ABI <0.9 or >1.3 [10].

Statistical Analysis

In tables 1 and 2, all continuous variables are presented as means $\pm$ SD. Skewed variables were $\log_{10}$-transformed before the following statistical analysis. Group comparisons were computed from ANOVA tests, and Scheffé tests were used for post hoc analysis. χ^2 tests were performed for comparison of categorical variables. In table 3, simple logistic regressions were used to examine the relationship between peripheral arterial disease and various parameters. In table 4, a multiple logistic regression analysis was used to determine the contribution of various factors to peripheral arterial disease after adjusting for age and gender. All analyses were performed with the statistical package for the Social Sciences program (SPSS for Windows, version 10; Chicago, Ill., USA). A p value of <0.05 was considered statistically significant.

Results

Among the 3 different stages of albuminuria, 233 normoalbuminuria, 69 microalbuminuria and 76 macroalbuminuria patients (with higher systolic and diastolic blood pressures, eGFR, triglycerides, fasting plasma glucose and HbA1C) had longer diabetes mellitus duration

Peripheral Arterial Disease, Diabetes, Albuminuria, eGFR

Table 1. Clinical and demographic characteristics of subjects with type 2 diabetes grouped by level of albuminuria

	Normoalbuminuria (n = 233)	Microalbuminuria (n = 69)	Macroalbuminuria (n = 76)	p value
Age[1], years	64.4 ± 7.8	64.7 ± 8.78	66.6 ± 9.3	0.125
Females[2], %	131 (56.2%)	40 (57.9%)	34 (44.7%)	0.172
BMI[1]	25.1 ± 3.2	25.2 ± 3.5	25.6 ± 6.1	0.608
Diabetes mellitus duration[1], years	11.3 ± 2.1	12.9 ± 2.5	14.8 ± 4.3	0.003[b, c]
SBP[1], mm Hg	127.2 ± 20.3	138.1 ± 22.2	140.1 ± 20.0	<0.001[a, b]
DBP[1], mm Hg	76.1 ± 10.4	80.9 ± 9.8	79.9 ± 12.9	0.009[b]
Creatinine[1], mg/dl	0.86 ± 0.22	0.89 ± 0.23	1.73 ± 0.73	<0.001[b, c]
eGFR[1], ml/min/1.73 m^2	75.8 ± 22.1	72.1 ± 22.6	42.5 ± 21.3	<0.001[b, c]
T-chol[1], mg/dl	180.6 ± 34.6	181.6 ± 33.3	189.0 ± 39.2	0.190
TG[1], mg/dl	110.1 ± 60.9	127.4 ± 88.8	143.8 ± 110.6	0.004[b]
LDL-C[1], mg/dl	104.0 ± 29.6	100.9 ± 32.0	106.9 ± 33.0	0.508
HDL-C[1], mg/dl	45.2 ± 12.8	45.6 ± 11.8	39.0 ± 10.6	<0.001[b]
FPG[1], mg/dl	145.2 ± 37.1	158.8 ± 47.4	167.2 ± 59.2	<0.001[b]
HbA1C[1], %	7.4 ± 1.1	8.0 ± 1.6	8.0 ± 1.4	<0.001[a, b]
Antilipid[2], %	41.7	42.8	54.8	0.330
ARB[2], %	68.2	94.2	95.3	0.027
ACEI[2], %	9.4	17.3	5.3	0.503
Anti-platelet agent[2], %	26.6	28.9	15.8	0.612
OAD[2], %	98.4	94.6	100	0.203
Insulin[2], %	5	14.7	31.7	<0.001
Smoking[2], %	3.4	16.7	19.5	0.002
Alcohol[2], %	6.7	5.5	9.8	0.744
CAD + CVA history[2], %	12.5	19.4	20.9	0.331
Retinopathy[2], %	58.5	69.1	80.6	0.005
ABI <0.9[2], %	12.0	10.1	31.6	<0.001
ABI >1.3[2], %	1.2	1.4	1.3	0.588
Pulse wave velocity[1], m/s	18.8 ± 7.2	22.5 ± 9.3	10.9 ± 6.5	0.789
Claudication[2], %	45.5	18.2	36.4	0.347
Ischemic ulcer[2], %	50.0	50.0	0	0.464

SBP = Systolic blood pressure; DBP = diastolic blood pressure; T-chol = total cholesterol; TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; FPG = fasting plasma glucose; ARB = angiotensin receptor blocker; ACEI = angiotensin-converting enzyme inhibitor; OAD = oral antidiabetic agents; CAD = coronary artery disease; CVA = cerebrovascular accident. [a] $p < 0.05$: normoalbuminuria vs. microalbuminuiria; [b] $p < 0.05$: normoalbuminuira vs. macroalbuminuria; [c] $p < 0.05$: microalbuminuria vs. macroalbuminuria.

[1] Values are presented as means ± SD; ANOVA for continuous variables.

[2] Values are presented as percentages for frequency distribution; χ^2 test for categorical variables.

with lowered creatinine and HDL-C levels as the albuminuria stage progressed. As expected, the higher the albuminuria level, the higher the prevalence of antihypertensive medication, especially angiotensin receptor blocker, and insulin usage, history of smoking, retinopathy and, in particular, peripheral arterial disease with a prevalence of 12.0, 10.1, and 31.6% in normoalbuminuria, microalbuminuria and macroalbuminuria patients, respectively (table 1).

However, in subjects with different stages of eGFR, i.e. in 103 patients with an eGFR of >90 ml/min/1.73 m^2, in 206 with an eGFR of 60–90 ml/min/1.73 m^2, in 146 with an eGFR of 30–60 ml/min/1.73 m^2 and in 23 with an eGFR of <30 ml/min/1.73 m^2 – aged 58.5 ± 6.0, 64.0 ± 7.3, 68.8 ± 8.1 and 68.5 ± 11.1 years, respectively – as the eGFR level decreased, age, creatinine and triglyceride levels, fasting plasma glucose, HbA1C, albuminuria level and diabetes mellitus duration were inversely increased, while the BMI was decreased. An increase in antihypertensive drug (especially angiotensin receptor blocker) and insulin usage, the presence of coronary artery disease and a cerebrovascular accident history are expected risk

Table 2. Clinical and demographic characteristics of subjects with type 2 diabetes grouped by level of eGFR

	eGFR, ml/min/1.73 m^2				p value
	>90 (n = 103)	60–90 (n = 206)	30–60 (n = 146)	<30 (n = 23)	
Age[1], years	58.5 ± 6.0	64.0 ± 7.3	68.8 ± 8.1	68.5 ± 11.1	<0.001[a–d]
Females[2], %	60.2	46.1	45.9	39.1	0.678
BMI[1]	26.8 ± 5.7	25.0 ± 3.4	24.3 ± 3.2	24.8 ± 3.3	<0.001[a, b]
Diabetes mellitus duration[1], years	8.2 ± 3.1	12.4 ± 3.9	14.9 ± 4.4	18.2 ± 6.5	0.002[b–f]
SBP[1], mm Hg	127.0 ± 26.5	129.9 ± 20.6	135.9 ± 24.9	144.5 ± 19.9	0.016[b, c]
DBP[1], mm Hg	80.7 ± 9.6	78.7 ± 11.2	77.5 ± 12.3	79.6 ± 10.9	0.357
Creatinine[1], mg/dl	0.75 ± 0.22	0.89 ± 0.29	1.19 ± 0.46	1.98 ± 0.91	<0.001[a–f]
T-chol[1], mg/dl	178.6 ± 32.4	184.4 ± 33.8	182.9 ± 38.0	191.9 ± 41.3	0.342
TG[1], mg/dl	125.6 ± 82.0	113.6 ± 66.3	112.3 ± 62.6	171.0 ± 166.2	0.004[e, f]
LDL-C[1], mg/dl	102.0 ± 28.3	109.3 ± 29.2	104.0 ± 35.0	99.4 ± 25.2	0.141
HDL-C[1], mg/dl	43.0 ± 11.0	44.5 ± 12.3	45.1 ± 13.1	38.0 ± 9.8	0.054
FPG[1], mg/dl	164.0 ± 53.9	153.1 ± 46.9	141.7 ± 43.3	173.7 ± 71.4	0.001[b]
HbA1C[1], %	8.0 ± 1.8	7.7 ± 1.5	7.4 ± 1.2	8.0 ± 1.5	0.018[b]
ACR log[1]	1.22 ± 0.61	1.28 ± 0.67	1.51 ± 0.81	2.54 ± 0.76	<0.001[b–f]
hsCRP[1], mg/dl	2.2 ± 3.1	2.1 ± 4.3	2.1 ± 6.0	4.0 ± 6.6	0.512
Antilipid[2], %	43.1	48.0	45.7	44.4	0.950
ARB[2], %	93.2	66.5	75.3	100.0	0.001
ACEI[2], %	9.7	10.2	10.9	8.7	0.627
Anti-platelet agent[2], %	33.0	19.4	32.2	52.2	0.432
OAD[2], %	100	94.3	100.0	100.0	0.036
Insulin[2], %	5.9	10.8	19.0	44.4	0.006
Smoking[2], %	5.9	11.4	11.4	11.1	0.703
Alcohol[2], %	5.9	7.8	7.6	0	0.823
CAD + CVA history[2], %	3.9	12.6	26.5	33.3	0.002
Retinopathy[2], %	54.1	64.0	63.6	84.2	0.086
ABI <0.9[2], %	11.7	11.2	21.9	30.1	<0.001
ABI >1.3[2], %	1.9	1.4	0	0	0.253
Pulse wave velocity[1], m/s	22.0 ± 11.6	17.9 ± 9.8	18.7 ± 8.4	20.4 ± 10.2	0.213
Claudication[2], %	15.4	38.5	30.8	15.4	0.066
Ischemic ulcer[2], %	33.3	0	66.7	0	0.569

SBP = Systolic blood pressure; DBP = diastolic blood pressure; T-chol = total cholesterol; TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; FPG = fasting plasma glucose; ACR = urine albumin/creatinine ratio; hsCRP = high-sensitivity C-reactive protein; ARB = angiotensin receptor blocker; ACEI = angiotensin-converting enzyme inhibitor; OAD = oral antidiabetic agents; CAD = coronary artery disease; CVA = cerebrovascular accident. [a] $p < 0.05$: eGFR >90ml/min/1.73 m^2 vs. eGFR 60–90 ml/min/1.73 m^2; [b] $p < 0.05$: eGFR >90 ml/min/1.73 m^2 vs. eGFR 30–60 ml/min/1.73 m^2; [c] $p < 0.05$: eGFR >90 ml/min/1.73 m^2 vs. eGFR <30 ml/min/1.73 m^2; [d] $p < 0.05$: eGFR 60–90 ml/min/1.73 m^2 vs. eGFR 30–60 ml/min/1.73 m^2; [e] $p < 0.05$: eGFR 60–90 ml/min/1.73 m^2 vs. eGFR <30 ml/min/1.73 m^2; [f] $p < 0.05$: eGFR 30–60 ml/min/1.73 m^2 vs. eGFR <30 ml/min/1.73 m^2.

[1] Values are presented as means ± SD; ANOVA for continuous variables.

[2] Values are presented as percentages for frequency distribution; χ^2 test for categorical variables.

factors in the later stage of chronic kidney disease. The prevalence of peripheral arterial disease was 11.7, 11.2, 21.9, and 30.1%, respectively, in patients with an eGFR of >90 ml/min/1.73 m^2, an eGFR of 60–90 ml/min/1.73 m^2, an eGFR of 30–60 ml/min/1.73 m^2 and an eGFR of <30 ml/min/1.73 m^2 (table 2).

Table 3 presents the simple logistic regression analysis of peripheral arterial disease with various parameters. Older age, higher systolic blood pressure, creatinine and albuminuria levels and lower GFR are significantly associated with peripheral arterial disease.

Table 4 presents the multivariate logistic regression analysis for peripheral arterial disease with different stages of albuminuria and eGFR. Age, sex, smoking and BMI were selected as potential confounders and were included in the adjusted models; macroalbuminuria was

Table 3. Simple logistic regression analysis for ABI <0.9 with each variable

	β	p	95% CI
Age	0.097	<0.001	1.069–1.137
Sex (female)	–0.484	0.060	0.372–1.021
BMI	0.020	0.492	0.964–1.079
Smoking	0.394	0.468	0.513–4.286
Diabetes mellitus duration	0.059	0.123	1.049–1.027
SBP	0.021	0.006	1.006–1.036
DBP	–0.022	0.166	0.949–1.009
T-chol	0.003	0.343	0.996–1.010
TG	0.001	0.519	0.998–1.004
LDL-C	0.003	0.521	0.995–1.011
HDL-C	–0.008	0.461	0.971–1.013
FPG	0.001	0.727	0.996–1.006
HbA1C	0.019	0.819	0.865–1.202
Creatinine	1.081	<0.001	1.886–4.603
eGFR >90 ml/min/1.73 m^2 (reference)			
eGFR 60–90 ml/min/1.73 m^2	–0.048	0.899	0.454–2.001
eGFR 30–60 ml/min/1.73 m^2	0.755	0.039	1.038–4.366
eGFR <30 ml/min/1.73 m^2	–2.026	0.003	1.738–13.673
Normoalbuminuria (reference)			
Microalbuminuria	–0.190	0.670	0.344–1.984
Macroalbuminuria	1.218	<0.001	1.810–6.309

SBP = Systolic blood pressure; DBP = diastolic blood pressure; T-chol = total cholesterol; TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; FPG = fasting plasma glucose; ACR = urine albumin/creatinine ratio.

the only variable showing a correlation, with a p value = 0.005 (95% CI 1.653–15.682). Age is also an independent factor associated with peripheral arterial disease. Systolic blood pressure and creatinine level were not included due to their relationship with the ABI and eGFR.

Discussion

The most important finding of our study is that the presence of macroalbuminuria is a stronger indicator of peripheral arterial disease than an eGFR <60 ml/min/1.73 m^2 in a Taiwanese diabetic population aged more than 50 years when both were present. Therefore, the decline of eGFR is an imperfect marker for peripheral arterial disease emphasizing the importance of determining albuminuria to predict the presence of peripheral arterial disease. These findings support current recommendations to regularly assess both albuminuria and eGFR in the clinical care of patients with diabetes [6, 7] with a sharp focus on interventions to prevent or treat CVD, especially peripheral arterial disease in the presence of albuminuria, impaired renal function, or both.

The National Kidney Foundation classification of chronic kidney disease is based primarily on eGFR levels, which differed from stages based on urinary albumin excretion. However, some studies have found decreased eGFR in the absence of increased urinary albumin excretion in some diabetic populations [11, 12]. Therefore, the American Diabetes Association suggested in 2007 that eGFR can be used to stage diabetic kidney disease [7]. The UK Prospective Diabetes Study reported that microalbuminuria alone may not provide optimal identification of patients with type 2 diabetes at a higher risk of renal impairment, therefore, a distinction between risk factors for albuminuria and those for renal impairment must be made [13]. In the UK Prospective Diabetes Study 74 with 15 years of follow-up, where renal impairment was defined as an eGFR of <60 ml/min/1.73 m^2 or a doubling of blood creatinine, risk factors for renal dysfunction in type 2 diabetes patients were increased insulin sensitivity, older age, female sex, a decreased white blood cell count and previous sensory neuropathy, while for albuminuria, risk factors were increased white blood cell count, plasma triglycerides, low-density lipoprotein cholesterol, HbA1C, male gender, smoking and previous retinopathy, whereas increased systolic blood pressure, urine albumin excretion, and plasma creatinine and Indian Asian ethnicity were risk factors for both albuminuria and renal impairment [13]. As compared with our study findings, we also confirmed the risk factors of increased systolic blood pressure, plasma creatinine and urine albumin for both renal impairment and albuminuria, and we also found increased triglycerides, fasting plasma glucose and HbA1C for both. Moreover, we also confirmed the risk factor of older age, and we found that a combination with coronary artery disease or cerebrovascular disease could be an important risk factor for developing renal dysfunction. With regard to the risk factors of albuminuria, we also confirmed smoking status and previous retinopathy, and found that increased diastolic blood pressure and decreased HDL-C were considered as risk factors for albuminuria. Therefore, determining peripheral arterial disease as a risk factor of renal impairment and albuminuria individually has its clinical importance, especially in patients with macroalbuminuria, which is a stronger predictor of peripheral arterial disease.

As one of the diabetic microvascular and macrovascular complications, diabetic nephropathy and peripheral arterial disease were both considered as a generalized en-

Table 4. Multivariate logistic regression analysis for ABI <0.9 with different variables

	β	p	Odds ratio	95% CI
Normoalbuminuria (reference)				
Microalbuminuria	−0.795	0.273	0.452	0.109–1.870
Macroalbuminuria	1.628	0.005	5.092	1.653–15.682
eGFR >90 ml/min/1.73 m^2 (reference)				
eGFR 60–90 ml/min/1.73 m^2	−0.477	0.499	0.620	0.156–2.475
eGFR 30–60 ml/min/1.73 m^2	−1.181	0.138	0.307	0.064–1.462
eGFR <30 ml/min/1.73 m^2	0.013	0.992	1.013	0.080–12.766
Sex	−0.197	0.678	0.821	0.323–2.085
Age	0.144	<0.001	1.154	1.081–1.233
Smoking	−0.329	0.695	0.720	0.139–3.717
BMI	0.052	0.314	1.053	0.952–1.164

dothelial dysfunction, which is caused by decreased nitric oxide bioavailability, and actually precedes the development of microalbuminuria [6, 14]. Albuminuria and impaired GFR may reflect different pathways of kidney damage. Albuminuria is a component of the metabolic syndrome and may present as a marker of increased risk of renal disease and CVD including peripheral arterial disease, which is associated with insulin resistance, widespread vascular damage and endothelial dysfunction, thus identifying susceptibility to disease in nonrenal vascular beds as diabetes progresses [15]. Impaired GFR may reflect loss of nephrons and parenchymal fibrosis that leads to CVD through accumulation of uremic toxins, impaired volume and blood pressure regulation and multiple metabolic abnormalities. Whether albuminuria and impaired GFR lead to CVD through distinct mechanisms, thus requiring distinct interventions, has not been established. However, both eGFR and albuminuria were confirmed to be independent risk factors for cardiovascular endpoints; they were already evident in patients with stage 2 chronic kidney disease and an eGFR between 60 and 89 ml/min/1.73 m^2, and they increased the all-cause mortality rate from 1.2 to 18.3% as renal function deteriorated from eGFR >90 ml/min/1.73 m^2 to eGFR 15–29 ml/min/1.73 m^2 [6].

Other studies have also shown a positive relationship between albuminuria and macrovascular complications, especially with regard to cardiovascular disease in diabetic populations, and some previous reports revealed the same relationship between peripheral arterial disease and renal insufficiency; however, only few showed a correlation between peripheral arterial disease and albuminuria [16, 17]. Tseng et al. [16] reported that the urinary ACR is associated with peripheral arterial disease and correlates inversely with the ABI in Taiwanese type 2 diabetic patients aged >65 years. Wattanakit et al. [17] observed that the presence of albuminuria, regardless of the magnitude, is an important risk factor for peripheral arterial disease in diabetic populations. Wattanakit et al. [18] also reported an increase in the incidence of peripheral arterial disease in those with chronic kidney disease. The association of chronic kidney disease and peripheral artery disease has been mentioned in some cross-sectional studies [19–23]. The NHANES III (Third National Health and Nutrition Examination Survey) reported that individuals with an eGFR <60 ml/min/1.73 m^2, hypertension, hypercholesterolemia and a self-reported cardiovascular disease history were more than twice as likely to have prevalent peripheral artery disease [18], while the HERS (Heart and Estrogen/Progestin Replacement Study) reported that individuals with an eGFR <60 ml/min/1.73 m^2 had an increased risk of developing a lower extremity peripheral artery disease event compared with those with an eGFR >60 ml/min/1.73 m^2, with multivariable relative risks of 1.63 (95% CI 1.04–2.54) and 3.24 (95% CI 1.20–8.78), respectively [24]. In accordance with the studies mentioned above, including the ARIC (Atherosclerosis Risk in Communities) study [18], we also confirmed that chronic kidney disease should be considered as a risk marker for peripheral artery disease; however, the possible pathways that link chronic kidney disease and peripheral artery disease still remain unclear. Which factor is more important if both albuminuria and chronic kidney disease were present is undetermined. In our study, peripheral arterial disease is strongly correlated individually with albuminuria and chronic kidney

disease, but if both factors coexisted, macroalbuminuria is more important than chronic kidney disease.

In our study, the prevalence of peripheral arterial disease in patients with normoalbuminuria and in those with an GFR >90 ml/min/1.73 m^2 was 12.0 and 11.7%, respectively. It is of note that the prevalence of diabetic nephropathy in type 2 diabetes appears to be higher in Asian populations than in Caucasian populations, but its underlying mechanisms are not clear [25]. The MAPS (Microalbuminuria Prevalence Study) reported a prevalence rate of 18.8 and 39.8% for macroalbuminuria and microalbuminuria, respectively, in Southeast Asia and the Western Pacific. An even higher number was noted for Taiwan, with a total prevalence rate for microalbuminuria and macroalbuminuria together of nearly 70% [26]. In this large population, diagnosis of peripheral arterial disease is important. However, since this high prevalence of peripheral arterial disease is also noted in patients with normoalbuminuria and in those with a GFR >90 ml/min/1.73 m^2, the ABI as a fundoscopic examination and the nerve conduction velocity test upon diagnosis of diabetes may be considered to be of equal importance.

The ABI has been found to be more accurate than other commonly used insensitive tests like the absence of peripheral pulses and the presence of claudication. In our study, the symptoms of claudication and ischemic ulcer did not correlate with the ABI. The ABI has to be 95% sensitive and almost 100% specific and has been validated against angiographically confirmed disease [27, 28]. Although calcified, poorly compressible vessels of elderly and diabetic patients may artificially elevate the values of the ABI; however, these are not prevalent enough to detract from the usefulness and effectiveness of the ABI in screening and diagnosing peripheral arterial disease in diabetic patients [10]. In our study, an ABI >1.3 was not significantly correlated with albuminuria nor with a decreased eGFR. The ABI may either be normal or abnormal in the presence of calcified and poorly compressible vessels, and these values may progress from high normal to elevated. This could underestimate the presence of peripheral arterial disease due to the limitation of the ABI measurement. Vascular laboratory evaluations including segmental pressures and pulse volume recordings, treadmill functional testing, systolic toe pressure and transcutaneous partial pressure of oxygen measurement can be considered for patients with poorly compressible vessels or for those with a normal ABI in whom peripheral arterial disease is highly suspected [14]. Duplex sonography, magnetic resonance angiogram and contrast angiography can be considered in patients for revascularization where anatomical localization of stenoses or occlusions is needed [10].

In summary, peripheral arterial disease is a major risk factor for lower extremity amputation, above all in a diabetic population. Determining the risk factors for developing peripheral arterial disease is important in the group of diabetic patients with renal outcomes, especially in patients with renal dysfunction with an eGFR of <60 ml/min/1.73 m^2 and in the stage of macroalbuminuria. Macroalbuminuria may be a more important risk factor for peripheral arterial disease than renal impairment, but controlling both risk factors may help reduce the progression of peripheral arterial disease. However, in our study population, there was a 12 and 10.1% prevalence of peripheral arterial disease in normoalbuminuria and microalbuminuria patients, respectively. Furthermore, in chronic kidney disease stages, the prevalence rate of peripheral arterial disease is 11.7 and 11.2% in patients with an eGFR of >90 ml/min/1.73 m^2 and in those with an eGFR of 60–90 ml/min/1.73 m^2, respectively. This shows the importance of performing the ABI in the whole diabetic kidney disease population.

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