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Risk Factors for Peripheral Arterial Disease among Patients with Chronic Kidney Disease

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Abstract

Patients with chronic kidney disease (CKD) have an increased risk of developing peripheral arterial disease (PAD). We examined the cross-sectional association between novel risk factors and prevalent PAD among patients with CKD. A total of 3,758 patients with an estimated glomerular filtration rate (eGFR) of 20–70 mL/min/1.73 m² who participated in the chronic renal insufficiency cohort (CRIC) study were included in the current analysis. PAD was defined as an ankle-brachial index <0.9 or a history of arm or leg revascularization. After adjustment for age, sex, race, cigarette smoking, physical activity, history of hypertension and diabetes, pulse pressure, high-density lipoprotein cholesterol, eGFR, and CRIC clinical sites, several novel risk factors were significantly associated with PAD. For example, odds ratios (95% confidence intervals) for a one standard deviation higher level of risk factors were 1.18 (1.08–1.29) for log-transformed high sensitivity-C reactive protein, 1.18 (1.08–1.29) for white blood cell count, 1.15 (1.05–1.25) for fibrinogen, 1.13 (1.03–1.24) for uric acid, 1.14 (1.02–1.26) for hemoglobin A1c, 1.11 (1.00–1.23) for log-transformed homeostasis model assessment-insulin resistance, and 1.35 (1.18–1.55) for cystatin C. In conclusion, these data indicate that inflammation, prothrombotic state, oxidative stress, insulin resistance, and cystatin C were associated with an increased

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prevalence of PAD in patients with CKD. Further studies are warranted to examine the causal effect of these risk factors on PAD in CKD patients.

Keywords

peripheral arterial disease; novel risk factors; chronic kidney disease

It is well established that older age, cigarette smoking, physical inactivity, hypertension, diabetes, and hypercholesterolemia play an important role in the initiation and development of atherosclerosis and its clinical manifestations, including PAD.¹ However, these traditional risk factors do not entirely explain the excess risk of PAD among some individuals, such as CKD patients.^{2,3} The identification of novel risk factors for PAD may help develop strategies for the prevention and treatment of PAD among patients with CKD. The Chronic Renal Insufficiency Cohort (CRIC) study is a large prospective cohort study of patients with varying degrees of CKD aimed at investigating risk factors for the progression of CKD and development of CVD.⁴ In the present analysis, we examine the association between a panel of novel CVD risk factors and prevalence of PAD after adjustment for established CVD risk factors in CKD patients.

Methods

The CRIC study participants include a racially and ethnically diverse group of men and women who were aged 21 to 74 years old and had CKD based on age-based estimated GFR (eGFR).⁴ A total of 3,939 CRIC participants were recruited between May 2003 and August 2008 from seven clinical centers in the US.⁵ Participants were identified through searches of laboratory databases, medical records, and referrals from health care providers. Patients with cirrhosis, HIV infection, polycystic kidney disease, or renal cell carcinoma, those on dialysis or recipients of a kidney transplant, or those taking immunosuppressant drugs were excluded. In the current analysis, participants with both a history of amputation and an ABI >0.9 (n=89), or an ABI >1.4 (n=92) were excluded due to uncertainty of their PAD status. After exclusion, 3,758 CRIC participants were included in the analysis.

This study was approved by the Institutional Review Boards for each of the participating clinical centers and the scientific and data coordinating center. Written informed consent was obtained from all participants. This study also conformed to the Health Insurance Portability and Accountability Act (HIPAA) guidelines.

All study data were collected by trained study staff during the CRIC clinical visits. All data collection procedures and equipment were standardized across study sites. A baseline medical history questionnaire was administered in which participants were queried about their prior history of PAD (claudication, amputation or angioplasty and procedures to open up blood vessels in arm or legs). Questionnaires also assessed demographic characteristics and lifestyle risk factors. Current smoker was defined as the participants who currently smoked and smoked more than 100 cigarettes in their lifetime. Former smoker was defined as the participants who smoked more than 100 cigarettes in their lifetime in the past. Alcohol drinker was defined as the participants who consumed one or more beverages containing alcohol each week over the previous year. Body weight and height were each measured twice and averaged for analysis. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the uppermost lateral border of the iliac crest with a Gulick II tape and repeated until two measures agreed within 1 centimeter. Three seated blood pressure (BP) measurements were obtained by trained and certified staff after at least 5 minutes of quiet rest. These

measurements were performed according to a standard protocol using an aneroid sphygmomanometer.⁶ The measurements were averaged as baseline systolic and diastolic BP for analysis. Pulse pressure was calculated by subtracting diastolic BP from systolic BP. Hypertension was defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and/or current use of antihypertensive medication.

ABI was obtained per standard protocol. After the participant rested supine for 5 minutes, systolic BP was measured in both arms with the appropriate-sized arm cuff. For each leg, systolic BP in each posterior tibial (PT) and dorsalis pedis (DP) artery was measured. All pressures were detected with a continuous-wave Doppler ultrasound probe. The leg-specific ABI was calculated by dividing the higher systolic BP in the PT or DP by the higher of the right or left brachial systolic BPs. PAD was defined as an ABI <0.9 or history of arm or leg revascularization in the current analysis.

Blood glucose, cholesterol, triglycerides, glycated hemoglobin (HbA1c), phosphate, calcium, alkaline phosphatase, total parathyroid hormone, uric acid, hemoglobin, albumin, bicarbonate, and white blood cell counts (WBC) were measured using standard laboratory methods. Serum high sensitive C-reactive protein (hsCRP), homocysteine, and cystatin C were measured by a particle enhanced immunonephelometry method. Fibrinogen was measured using an immunochemical reaction method. Serum myeloperoxidase was measured using a chemiluminescent microparticle immunoassay (Abbott Diag. Architect ci8200). Urinary albumin was measured by radioimmunoassay (RIA). Diabetes was defined as a fasting glucose ≥ 126 mg/dL, a random glucose ≥ 200 mg/dL, and/or use of insulin or other anti-diabetic medication. Estimated-GFR (eGFR) was calculated using the re-expressed Modification of Diet in Renal Disease (MDRD) equation after calibrating serum creatinine measurements to isotope dilution mass spectrometry-traceable values.⁷ A homeostasis model assessment (HOMA) was calculated to evaluate insulin resistance using the following formula: fasting serum insulin (μ U/mL) $\times$ fasting plasma glucose (mmol/L) / 22.5.⁸ Albumin corrected calcium levels were calculated as follows: serum calcium (mg/dL) + $[0.8 \times (4 - \text{serum albumin (g/dL)})]$.⁹ All laboratory measurements were performed at the CRIC Central Clinical Laboratory at the University of Pennsylvania.

Baseline characteristics of participants were summarized as means (standard deviation, SD) for continuous variables and percentages for categorical variables by PAD status. Statistical significance was tested using ANOVA for continuous variables and the χ^2 test for categorical variables. Multiple logistic regression analyses were used to explore the associations of PAD with traditional and novel CVD risk factors. In the multiple traditional risk factor model, all demographic variables and traditional risk factors which were significant in univariate analysis, including age, sex, race/ethnicity, cigarette smoking, history of hypertension and diabetes, physical activity (total metabolic equivalent [MET]/week), HDL-cholesterol, pulse pressure, eGFR, and 13 CRIC clinic sites were simultaneously included. In the multivariable analysis of novel CVD risk factors, two sets of covariables were adjusted. First, demographic variables, including age, sex, race, and CRIC clinical sites were adjusted. Then, traditional CVD risk factors, including cigarette smoking, physical activity, diabetes, hypertension, HDL-cholesterol, pulse pressure, and eGFR were included. Odds ratios and 95% confidence intervals (CI) of PAD associated with categorical variables or one SD increase in continuous variables were presented. For those novel risk factors which were not normally distributed, including HOMA-insulin resistance, hsCRP, total parathyroid hormone, and myeloperoxidase, the log transformation was taken. All analyses were conducted using SAS v9.1 (Cary, NC). All p-values were two-sided and statistical significance was defined as $p < 0.05$.

Results

Characteristics of CRIC participants by PAD status are provided in Table 1.

The age-gender-race-clinic-adjusted prevalence of PAD according to eGFR levels by diabetes status is displayed in figure 1. There was a significant, graded, and inverse association between eGFR and prevalence of PAD among patients with and without diabetes (p-value for trend <0.0001 for both groups). The prevalence of PAD was also significantly higher in patients with diabetes compared to those without, stratified by eGFR categories (p-value for group difference <0.0001).

The odds ratios (95% CI) of PAD associated with traditional risk factors from a multivariable model are shown in Table 2. Age, black race, former and current cigarette smoking, history of diabetes, and pulse pressure were positively and significantly associated with the odds of PAD, while physical activity, HDL-cholesterol, and eGFR were inversely and significantly associated with the odds of PAD.

The age-gender-race-clinic-adjusted and multivariate-adjusted odds ratios of PAD associated with novel risk factors are shown in Table 3. After adjusting for demographic variables, higher levels of phosphate, calcium phosphate product, alkaline phosphatase, log-transformed total parathyroid hormone, log-transformed hsCRP, WBC, homocysteine, fibrinogen, uric acid, log-transformed myeloperoxidase, HbA1c, log-transformed HOMA-insulin resistance, cystatin C and urine albuminuria were significantly associated with higher odds of PAD, while higher levels of albumin and hemoglobin were significantly associated with lower odds of PAD. After further adjusting for multiple traditional CVD risk factors, hsCRP, WBC, fibrinogen, uric acid, myeloperoxidase, HbA1c, HOMA-insulin resistance, and cystatin C remained significantly associated with higher odds of PAD.

We tested the interactions between diabetes and novel risk factors on PAD. Among 16 tested novel risk factors, we found 2 significant interactions: odds ratios of PAD associated with HbA1c were 1.52 (95% CI 0.98, 2.38) in diabetic patients and 1.10 (95% CI 0.98, 1.22) in non-diabetic patients (p=0.02 for interaction); odds ratios of PAD associated with urine albumin excretion were 0.72 (95% CI 0.50, 1.03) in diabetic patients and 1.12 (95% CI 1.10, 1.53) in non-diabetic patients (p=0.02 for interaction). However, these interactions were not statistically significant after multiple comparisons were taken into account. In addition, there was no significant interaction between parathyroid hormone and cystatin C (p= 0.09).

Discussion

The present study identified a significant association between several novel CVD risk factors and PAD among patients with CKD. The prevalence of PAD increased with higher levels of hsCRP, WBC, fibrinogen, uric acid, myeloperoxidase, HbA1c, HOMA-insulin resistance, and cystatin C. These relationships were independent of traditional CVD risk factors. Our findings are noteworthy, because this is the first study to report a significant association of hsCRP, WBC, fibrinogen, uric acid, myeloperoxidase, HbA1c, HOMA-insulin resistance, and cystatin C with the prevalence of PAD among a large sample of CKD patients. In addition, numerous CVD risk factors were measured and adjusted in the multivariable analyses. Furthermore, careful measures of study exposure and outcome variables allowed for precise estimation of the association.

These findings have important clinical and public health implications because patients with CKD have an increased risk of developing PAD.^{10,11} Identifying novel risk factors for PAD may help develop strategies for the prevention and treatment of PAD among patients with CKD. The current study provides new and important information on novel risk factors for

PAD among CKD patients. Wattanakit et al reported that reduced kidney function was significantly associated with development of PAD in the Atherosclerosis Risk in Communities (ARIC) study.¹⁰ Ix et al also reported an inverse association of eGFR with risk of a ABI<0.9 in an elderly population.¹¹ Our study indicated that there was a significant inverse relationship between eGFR levels and prevalence of PAD in CKD patients with and without diabetes.

The underlying reason for the increased risk of PAD among patients with CKD is not well understood. In this study, we found that traditional risk factors such as age, black race, cigarette smoking, diabetes, and pulse pressure were associated with an increased prevalence of PAD among CKD patients. In addition, we found that higher physical activity and serum HDL-cholesterol level were associated with lower prevalence of PAD.

Allison et al examined the association between novel risk factors and PAD among general populations and reported that one standard deviation higher levels of homocysteine, CRP, and fibrinogen were associated with increased odds for PAD of 1.15, 1.29, and 1.31-fold, respectively, after adjustment for traditional risk factors for PAD.¹² Recently, Pande and colleagues also reported that CRP and insulin resistance were associated with increased risk of PAD in the general population.¹³ In addition, Shankar et al reported that higher serum uric acid levels were positively associated with PAD, independent of smoking, BMI, hypertension, diabetes, serum total cholesterol, serum creatinine, and other confounders among 3,987 National Health and Nutrition Examination Survey 1999-2002 participants.¹⁴ Very few studies have examined the novel risk factors for PAD in patients with CKD. Jaar et al reported that homocysteine was associated with risk of PAD in incident-dialysis patients.¹⁵ To our knowledge, this study is the first investigation into novel risk factors for PAD in predialysis CKD patients. Our data suggested that hsCRP, WBC, fibrinogen, uric acid, myeloperoxidase, HbA1c, HOMA-insulin resistance, and cystatin C increase the prevalence of PAD in CKD patients independent of traditional CVD risk factors including hypertension, diabetes and kidney function.

Both hsCRP and fibrinogen are circulating acute-phase reactants that increase manifold during the inflammatory response to tissue injury or infectious triggers.¹⁶ WBC is also an inflammatory marker. Our study suggests that systemic inflammation might contribute to development of PAD in CKD patients.

Uric acid is one of the major plasma antioxidants, but it could also manifest pro-oxidant properties and promote lipid oxidation in vascular tissue.^{17,18} In addition, an experimental study suggested that uric acid may induce inflammation and reduce nitric oxide release from vascular cells.¹⁹ It is likely that uric acid increases the risk of PAD in CKD patients through the mechanism of oxidative stress, inflammation, and endothelial dysfunction. Further study is warranted to examine this significant issue.

Hemoglobin A1c and HOMA-insulin resistance were associated with PAD in our study independent of a history of diabetes. Previous data suggested that there was a positive and independent association between HbA1c and PAD risk in adults with or without diabetes.^{20,21} In addition, insulin resistance was associated with PAD in the US general population.¹³ These data combined with our findings support the notion that higher levels of HbA1c and insulin resistance are associated with an increased risk of PAD in CKD patients.

A previous study suggested that elevated cystatin C is independently predictive of incident PAD events among elderly patients.²² Our data indicate that the association of cystatin C with prevalence of PAD is independent of creatinine-based eGFR, which suggests that cystatin C may represent residual kidney function that is not precisely captured by serum creatinine. In addition, cystatin C was associated with inflammation and might be a marker

of systemic inflammation.²³ The causal relationship of cystatin C to PAD remains to be explored.

Potential limitations of our study should be noted. First, this cross-sectional analysis cannot establish a temporal relationship between the risk factors and PAD. Some of these risk factors could be an effect of the disease itself rather than a cause. Therefore, future longitudinal study and clinical trials are warranted to establish a causal relationship. In addition, serum creatinine-based eGFR was used to define renal function in our study. Although inulin or iothalamate clearance techniques may provide a more sensitive estimate of renal function, serum creatinine-based eGFR has been used widely in large epidemiologic studies and in clinical practice. As such, the findings from our study are applicable to clinical and public health practice settings. Furthermore, the insulin resistance was not measured using the gold standard method, i.e., the hyperinsulinemic-euglycemic clamp, as this method is impractical in a large-study setting. HOMA-insulin resistance level has been found to be an appropriate surrogate indicator for the insulin sensitivity clamp across a broad spectrum of insulin sensitivity and glucose tolerance levels and is considered to be suitable for use in epidemiologic studies by the American Diabetes Association.²⁴ HOMA-insulin resistance has also been validated among CKD patients.²⁵

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Figure 1. Age-gender-race-clinical site-adjusted prevalence of peripheral artery disease according to eGFR levels in patients with chronic kidney disease by diabetes status (p value for trend <0.0001 for both groups)

Table 1
Demographic, lifestyle, clinical and biochemical characteristics of study participants according to peripheral artery disease

Variables	Peripheral Artery Disease		P-value
	Yes (n=754)	(n=300)	
Age (years)	62.2 (9.1)	57.2 (11.2)	<0.0001
Male	53.4%	54.6%	0.58
Race/ethnicity			
White	39.5%	48.0%	
Black	50.1%	40.4%	<0.0001
Other	10.3%	11.6%	
High school education	71.4 %	81.8%	<0.0001
Physical activity (MET/week)	165.07(119.8)	208.04(150.7)	<0.0001
Cigarette smoking			
Never smoker	29.6%	48.6%	
Former smoker	51.1%	39.6%	<0.0001
Current smoker	19.4%	11.8%	
Alcohol drinker	14.6%	22.1%	<0.0001
Hypertension	93.2%	84.1%	<0.0001
Diabetes mellitus	64.6%	42.3%	<0.0001
Body mass index (kg/m ²)	32.9 (8.6)	31.8 (7.6)	0.0003
Waist circumference (cm)	108.3 (17.9)	105.0 (17.4)	<0.0001
Pulse pressure (mmHg)	65.1 (19.8)	54.5 (18.3)	<0.0001
High density lipoprotein cholesterol (mg/dL)	45.3 (14.3)	48.2 (15.8)	<0.0001
Low-density lipoprotein cholesterol (mg/dL)	99.7 (34.8)	103.9 (35.3)	0.004
Calcium (mg/dL)	9.16 (0.56)	9.20 (0.50)	0.07
Phosphate (mg/dL)	3.83 (0.71)	3.68 (0.65)	<0.0001
Calcium phosphate product	35.0 (6.64)	33.9 (6.21)	<0.0001
Alkaline phosphatase (U/L)	96.7 (36.4)	90.5 (34.3)	<0.0001
Log [total parathyroid hormone (pg/mL)]	4.2 (0.75)	4.0 (0.69)	<0.0001
Log [high sensitivity C-reactive protein (mg/L)]	1.20 (1.26)	0.87 (1.26)	<0.0001
White blood cells (thousand/uL)	7.08 (3.12)	6.45 (1.97)	<0.0001
Homocysteine (μmol/L)	16.6 (6.43)	14.6 (5.94)	<0.0001
Fibrinogen (mg/dL)	4.52 (1.29)	4.05 (1.16)	<0.0001
Uric acid (mg/dL)	7.82 (1.98)	7.29 (1.89)	<0.0001
Log [myeloperoxidase (pmol/L)]	4.82 (0.97)	4.65 (1.18)	0.0004
Serum albumin (g/dL)	3.87 (0.48)	3.97 (0.46)	<0.0001
Hemoglobin (g/dL)	12.2 (1.71)	12.8 (1.77)	<0.0001
Hemoglobin A1c (%)	7.07 (1.53)	6.51 (1.53)	<0.0001
Homeostasis model assessment-insulin resistance	8.1 (9.7)	6.2 (8.1)	<0.0001
Estimated glomerular filtration rate (ml/min/1.73m ²)	38.6 (12.2)	44.1 (13.6)	<0.0001
Cystatin C (mg/L)	1.74 (0.56)	1.45 (0.52)	<0.0001

Variables	Peripheral Artery Disease		P-value
	Yes (n=754)	(n=300)	
Urinary albumin (g//24-hours)	0.91 (2.14)	0.6 (1.43)	<0.001

Table 2
Odds ratios (95% confidence intervals) of peripheral artery disease associated with traditional cardiovascular risk factors

Variables	Odds Ratios (95% CI) [*]	P-value
Age (5 year)	1.19 (1.13, 1.25)	<0.0001
Male	0.83 (0.69, 1.01)	0.065
Race/ethnicity		
White	1.00 (reference)	
Black	1.24 (1.02, 1.51)	0.098
Other	1.01 (0.68, 1.49)	
Cigarette smoker		
Never smoker	1.00 (reference)	
Former smoker	1.78 (1.46, 2.17)	<0.0001
Current smoker	2.68 (2.06, 3.49)	
Diabetes mellitus	1.75 (1.45, 2.12)	<0.0001
Hypertension	1.15 (0.83, 1.60)	0.41
Physical activity (146 METs/week [†])	0.87 (0.78, 0.97)	0.01
High density lipoprotein cholesterol (16 mg/dL [†])	0.83 (0.74, 0.91)	0.0003
Pulse pressure (19 mmHg [†])	1.30 (1.18, 1.43)	<0.0001
Estimated glomerular filtration rate (14 ml/min per 1.73 m ² [†])	0.74 (0.67, 0.82)	<0.0001

* All co-variables listed in the table were adjusted simultaneously in addition to 13 CRIC clinic sites.

[†] One standard deviation.

Table 3
Odds ratios (95% confidence intervals) of peripheral artery disease associated with novel cardiovascular risk factors

Variables*	Age-sex-race-clinical site-adjusted		Multivariable-adjusted [†]	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Corrected calcium (0.5 mg/dL)	1.01 (0.93, 1.10)	0.76	0.99 (0.91, 1.08)	0.87
Phosphate (0.7 mg/dL)	1.24 (1.14, 1.35)	<0.0001	1.03 (0.93, 1.13)	0.57
Calcium phosphate product (6.6)	1.23 (1.13, 1.35)	<0.0001	1.02 (0.93, 1.13)	0.64
Alkaline phosphatase, (34.8 U/L)	1.13 (1.04, 1.22)	0.003	1.01 (0.92, 1.10)	0.87
Log [total parathyroid hormone (0.70 pg/mL)]	1.24 (1.13, 1.35)	<0.0001	1.03 (0.93, 1.14)	0.58
Log [high sensitivity C-reactive protein (1.3mg/L)]	1.24 (1.14, 1.35)	<0.0001	1.18 (1.08, 1.29)	0.0003
White blood cell (2.3 thousand/uL)	1.36(1.25, 1.49)	<0.0001	1.18 (1.08, 1.29)	0.0004
Homocysteine (6.1 μ mol/L)	1.20 (1.11, 1.31)	<0.0001	1.08 (0.98, 1.19)	0.11
Fibrinogen (1.2mg/dL)	1.38 (1.27, 1.50)	<0.0001	1.15 (1.05, 1.25)	0.003
Uric acid (1.9 mg/dL)	1.24 (1.13, 1.35)	<.0001	1.13 (1.03, 1.24)	0.01
Log[myeloperoxidase (1.1 pmol/L)]	1.17 (1.04, 1.30)	0.006	1.11 (1.00, 1.23)	0.056
Serum albumin (0.5g/dL)	0.82 (0.75, 0.89)	<0.0001	0.98 (0.89, 1.08)	0.74
Hemoglobin (1.8 g/dL)	0.76 (0.69, 0.84)	<0.0001	0.96 (0.86, 1.07)	0.45
Hemoglobin A1C (1.5%)	1.35 (1.25, 1.46)	<0.0001	1.14 (1.02, 1.26)	0.017
Log [HOMA- insulin resistance (0.8)]	1.29 (1.19, 1.41)	<0.0001	1.11 (1.00, 1.23)	0.048
Cystatin C (0.5 mg/L)	1.56 (1.43, 1.69)	<0.0001	1.35 (1.18, 1.55)	<0.0001
Urine albumin (1.6 g/24 hours)	1.27 (1.17, 1.37)	<0.0001	1.06 (0.97, 1.15)	0.21

* One standard deviation

[†] Adjusted for age, gender, race/ethnicity, cigarette smoking, physical activity, diabetes, hypertension, HDL-cholesterol, pulse pressure, eGFR, and CRIC clinic sites.