Kidney Function and Risk of Peripheral Arterial Disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study

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Chronic kidney disease (CKD) is associated with an increased risk for cardiovascular disease, but its association with peripheral arterial disease (PAD) is unclear. With the use of data from the Atherosclerosis Risk in Communities (ARIC) Study, 14,280 middle-aged adults were categorized on the basis of estimated GFR ≥90, 60 to 89, and 15 to 59 ml/min per 1.73 m^2 for normal kidney function, mildly decreased kidney function, and stages 3 to 4 CKD, respectively. Incident PAD was defined as a new onset of ankle-brachial index <0.9 assessed at regular examinations, new intermittent claudication assessed by annual surveillance, or PAD-related hospital discharges. Incidence rates and relative risks (RR) for PAD were compared across these categories. During a mean follow-up time of 13.1 yr (186,616 person-years), 1016 participants developed PAD. The incidence rates per 1000 person-years were 4.7, 4.9, and 8.6 for the normal kidney function, mildly decreased kidney function, and CKD groups, respectively. Compared with participants with normal kidney function, the age-, gender-, race-, and ARIC field center–adjusted RR for PAD was 1.04 (95% confidence interval [CI] 0.91 to 1.18) for those with mildly decreased kidney function and 1.82 (95% CI 1.34 to 2.47) for those with CKD. After additional adjustment for cardiovascular disease risk factors, an increase in risk for incident PAD still was observed in participants with CKD, with a multivariable adjusted RR of 1.56 (95% CI 1.13 to 2.14). Patients with CKD are at increased risk for incident PAD. Development of strategies for screening and prevention of PAD in this high-risk population seems warranted.

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Estimates from the Third National Health and Nutrition Examination Survey (NHANES III) suggest that 8 million people (4.5% of the US population) have chronic kidney disease (CKD), defined by estimated GFR (eGFR) between 15 and 59 ml/min per 1.73 m^2, and approximately 300,000 people (0.1%) have ESRD, defined by eGFR <15 ml/min per 1.73 m^2 or dialysis treatment (1). It now is recognized that the clinical course of CKD often is complicated by cardiovascular disease (CVD) (2,3) and death (4,5), independent of established risk factors.

Patients with non–dialysis-dependent CKD also might be at increased risk for developing peripheral arterial disease (PAD). Most previous studies that investigated this relationship focused only on patients with dialysis-dependent ESRD, and studies of populations with non–dialysis-dependent CKD largely have been examined in cross-sectional surveys (6,7) or have either not included PAD as an outcome (2,3) or included PAD in a composite CVD outcome (5,8). To our knowledge, only one previous study prospectively examined the association between CKD and incident PAD (9). This single study cohort included only postmenopausal women with documented coronary heart disease (CHD). We therefore conducted a prospective study to investigate whether level of kidney function is inversely related to risk for PAD.

Materials and Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study is a large, prospective, community-based study of the etiology and natural history of atherosclerosis and CVD. The study cohort comprised 15,792 participants who were aged 45 to 64 yr at baseline in 1987 to 1989 and were recruited from four US communities: Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD. The cohort underwent reexamination visits at roughly 3-yr intervals, with a 93% return rate for visit 2 (1990 to 1992), 86% for visit 3 (1993 to 1995), and 81% for visit 4 (1996 to 1998). Detailed descriptions of the ARIC study design and objectives have been published elsewhere (10).

Of the 15,792 ARIC participants, we included 14,390 who had serum creatinine measured and no history of PAD (ankle-brachial index [ABI] ≥0.9) or intermittent claudication at baseline. We excluded 97 participants whose race was other than black or white and an additional 13

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participants whose eGFR was <15 ml/min per 1.73 m^2, leaving a total of 14,280 participants for the final analyses. Most participants had nearly complete data.

Ascertainment of the Level of Kidney Function

Serum creatinine was measured using the modified kinetic Jaffe method. Because a number of factors, such as age, ethnicity, and gender, can influence serum creatinine, the level of kidney function was ascertained by eGFR, which was calculated using the formula that was developed and validated in the Modification of Diet in Renal Disease (MDRD) study (11). The MDRD formula is as follows:

$$eGFR = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

For use in this formula, serum creatinine was calibrated by subtraction of 0.24 (12). We assigned participants with a physiologically implausible high eGFR ($n = 3$) to a maximum of 200 ml/min per 1.73 m^2. eGFR was divided into the following categories on the basis of the National Kidney Foundation guidelines: eGFR >90 ml/min per 1.73 m^2 for normal kidney function, eGFR between 60 and 89 ml/min per 1.73 m^2 for mildly decreased kidney function, and eGFR between 15 and 59 ml/min per 1.73 m^2 for stages 3 to 4 CKD, which hereafter is referred to as CKD.

Ascertainment of Incident PAD

In individuals without prevalent PAD, PAD incidence was characterized by one of the following criteria: (*1*) A new ABI < 0.9 at either visit 3 or 4; (*2*) new intermittent claudication based on Rose Questionnaire (13); or (*3*) a hospital discharge diagnosis of PAD, leg amputation, or leg revascularization procedures (leg endarterectomy, aorto-iliac-femoral bypass surgery, or leg bypass surgery).

ABI was measured on nearly all participants at ARIC visit 1 (96.4%), but only a random sample of participants were invited for ABI measurement during visits 3 ($n = 4197$) and 4 ($n = 5882$). At visit 1, ABI was computed by dividing the average of ankle systolic BP (SBP) measurements by the average of brachial SBP measurements (14). Using the Dinamap 1846 SX automated oscillometric device (Criticon, Tampa, FL), trained technicians measured two ankle BP, taken 5 to 8 min apart, at the posterior tibial artery in a randomly selected leg while the participant was prone. This automated BP measurement device has high validity compared with the standard Doppler ultrasound measurement and high repeatability (15). Two brachial artery BP were measured, usually in the right arm, with the participant supine. At visits 3 and 4, the ABI was defined as the ratio of a single ankle SBP to a single brachial BP, both measured with the participant supine (16).

Interviewers contacted participants annually by telephone to identify intermittent claudication symptoms and all hospitalizations. The Rose Questionnaire (13) was used to evaluate whether participants had developed intermittent claudication, which was defined as exertional leg pain relieved within 10 min by resting. Depending on the study, it has 9 to 92% sensitivity and 95.9 to 100% specificity in identifying PAD (17). When a hospitalization had occurred, a trained abstractor obtained and recorded all *International Classification of Disease, Ninth Revision* hospital discharge diagnoses. All records with an *International Classification of Disease, Ninth Revision* code of 443.9 (claudication, peripheral arterial disease not otherwise specified, peripheral angiopathy not otherwise specified, spasm of artery), 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below-knee amputation), 84.17 (above-knee amputation), 38.18 (leg endarterectomy), 39.25 (aorto-iliac-femoral bypass), and 39.29 (leg bypass surgery) were considered to be hospitalized PAD.

Measurement of Baseline Risk Factors

After informed consent, the ARIC participants underwent a standardized medical history and examination that included interviews and a fasting venipuncture. Participants were classified as never, former, or current alcohol drinkers. Pack-years of smoking were calculated by multiplying the average number of cigarettes per day by the number of years smoked and dividing by 20. Physical activity was assessed using the Baecke sports questionnaire, with scores ranging from 1 (low) to 5 (high), and participants were categorized as low (<2) moderate (2 to 4), or high (≥4) (18). Participants were asked to bring all current medications to each ARIC study visit. Medication types were recorded, including cholesterol-lowering medications, β blockers, angiotensin-converting enzyme inhibitors, or other antihypertensive medications. Anthropometrics, including weight and height, were obtained while the participant was wearing a scrub suit. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Fasting blood samples were drawn from an antecubital vein for measurement of hemostatic factors, lipids, glucose, and chemistries. Laboratory assays were performed in standardized research laboratories except for white blood cell count, which was measured in local laboratories. The ARIC Central Lipid Laboratory's methods for triglycerides, HDL cholesterol, and calculated LDL cholesterol have been reported (19). The ARIC Central Hemostasis Laboratory measured fibrinogen, factor VII, and factor VIII using published methods (20).

Prevalent CHD was defined as a self-reported history of physician-diagnosed myocardial infarction (MI), coronary artery bypass surgery, coronary angioplasty, or a previous MI by electrocardiogram. SBP and diastolic BP (DBP) were measured three times using a random-zero sphygmomanometer, and the average of the last two measurements was used for analysis. Prevalent hypertension was defined as seated DBP ≥90 mmHg, SBP ≥140 mmHg, or use of antihypertensive medications within the past 2 wk. Prevalent diabetes was defined as a fasting serum glucose level ≥7.0 mmol/L (126 mg/dl), nonfasting glucose level ≥11.1 mmol/L (200 mg/L), participant report of a physician diagnosis of diabetes, or current use of any diabetes medication.

Statistical Analyses

We analyzed incident PAD through 2002. For those who developed PAD, we calculated the length of follow-up from the baseline examination to the time of first PAD diagnosis. The date of event was based on the earliest date of visit 3 or 4 (when ABI was <0.9), date when intermittent claudication first was classified, or hospitalization discharge date. We did not exclude participants with missing ABI measurement at visit 3 or 4 or both, as long as they continued annual telephone contacts to allow intermittent claudication and PAD-related revascularization procedures to be ascertained. For participants without a PAD event, follow-up ended on the date of death, date of last known contact, or December 31, 2002, whichever came first.

We compared baseline CVD risk factors of the participants who did and did not develop PAD during follow-up using ANOVA, adjusted for age, gender, race, and ARIC field center. Similarly adjusted incidence rates per 1000 person-years were estimated for the three categories of kidney function using Poisson regression. Kaplan-Meier curves were created to compare the cumulative probability of remaining free of PAD events for each category of CKD. With normal kidney function as a reference group, proportional hazards regression was used to calculate relative risks (RR) and 95% confidence intervals (CI) for incident PAD, adjusting for age, gender, race, and ARIC field center. Multiple models were constructed for further exploration of pathways that mediate CKD and PAD. Model 2 was adjusted for traditional CVD risk factors, including diabetes, LDL and HDL cholesterol, triglycer-

ides, prevalent CHD, pack-years of cigarettes, BMI, physical activity, use of alcohol, and use of cholesterol medication; model 3 was adjusted for all covariates in model 2 plus SBP and DBP and use of antihypertensive medication; and model 4 was adjusted for all covariates in model 2 plus inflammatory and procoagulant markers (fibrinogen, factor VII, factor VIII, and white blood cell count). To examine the dosage-response relation between the risk for PAD and eGFR, we fitted a restricted cubic spline regression model to the data. This approach has advantages over the categorical analysis because it does not assume the form of the exposure–disease relation and avoids the problem of placing eGFR levels with different degrees of PAD risk in the same category (21,22). All statistical analyses were conducted using SAS software version 8.2 (SAS Institute, Cary, NC).

Results

Among the 14,280 participants (mean age 54 yr), the mean visit 1 eGFR was 93.1 ml/min per 1.73 m^2 (SD 20.5). Among those with CKD, 366 (97.3%) had eGFR between 30 and 59 ml/min per 1.73 m^2, and 10 (2.7%) participants had eGFR between 15 and 29 ml/min per 1.73 m^2. The mean eGFR among participants who met National Kidney Foundation criteria for CKD was 52.6 ml/min per 1.73 m^2 (SD 7.7).

During a mean follow-up time of 13.1 yr (186,616 person-years), 1016 participants developed PAD. Of these, 576 were detected only by low ABI at visit 3 or 4 (271 [47.0%], 290 [50.3%], and 15 [2.6%] had normal kidney function, mildly decreased kidney function, and CKD at baseline, respectively). Of those with clinically recognized disease, 308 had Rose Questionnaire intermittent claudication (130, 163, and 15 had normal kidney function, mildly decreased kidney function, and CKD at baseline, respectively), and 242 had PAD-related leg amputations or revascularization procedures (96, 124, and 22 had normal kidney function, mildly decreased kidney function, and CKD at baseline, respectively). Compared with participants without incident PAD, those who developed PAD were more likely to be older and have higher prevalences of diabetes, cholesterol medication use, and CHD as well as greater mean pack-years of cigarette use, alcohol intake, LDL cholesterol, triglycerides, fibrinogen, and BMI and lower mean values of HDL cholesterol, ABI, and physical activity score (Table 1). This worse risk factor profile also was present for all subgroups of incident PAD (ABI <0.9, intermittent claudication, or PAD-related revascularization procedures) compared with PAD-free counterparts (data not shown).

The age-, gender-, race-, and ARIC field center–adjusted PAD incidence rates per 1000 person-years were 4.7, 4.9, and 8.6 for the normal kidney function, mildly decreased kidney function, and CKD groups, respectively (Table 2). Kaplan-Meier curves confirmed a greater probability of remaining free of PAD in participants with normal kidney function than in those with CKD (Figure 1). The probability of remaining free of PAD was not statistically significantly different between those with mildly decreased kidney function and those with normal kidney function ($P = 0.17$).

Table 1. Adjusted baseline characteristics of study population by incident PAD status: The ARIC Study, 1987[a]

Baseline Risk Factor	Incident PAD		*P*
	Yes (n = 1016)	No (n = 13,264)	
Age (yr)	56	54	<0.0001
Male (%)	45	45	0.73
White race (%)	76	74	0.20
Diabetes (%)	22.0	10.6	<0.0001
Prevalent hypertension (%)	43.0	33.2	<0.0001
Prevalent CHD (%)	10.7	4.2	<0.0001
Pack-years of cigarette smoking among current smokers	23.1	15.0	<0.0001
Mean LDL cholesterol (mg/dl)	142	137	<0.0001
Mean HDL cholesterol (mg/dl)	48	52	<0.0001
SBP (mmHg)	125	121	<0.0001
DBP (mmHg)	74	74	0.92
Mean triglycerides (mg/dl)	146	129	<0.0001
Fibrinogen (mg/dl)	321	300	<0.0001
BMI (kg/m^2)	28.4	27.6	<0.0001
Mean ankle-brachial index	1.10	1.15	<0.001
Mean eGFR (ml/min per 1.73 m^2)	92	93	0.17
Sport index score (out of 5)	2.37	2.45	0.0023
Current alcohol drinkers (%)	35.1	39.1	0.007
Use of cholesterol medication (%)	4.8	2.6	<0.0001
Use of anti-hypertensive medication (%)	39	29	<0.0001

[a]Adjusted for age, gender, race, and Atherosclerosis Risk in Communities (ARIC) field center. BMI, body mass index; CHD, coronary heart disease; DBP, diastolic BP; eGFR, estimated GFR; PAD, peripheral arterial disease; SBP, systolic BP.

Table 2. Rates and relative risks (95% confidence intervals) of incident PAD events by level of eGFR: The ARIC Study, 1987 to 2002

Parameter	eGFR ≥90 (ml/min per 1.73 m^2) (n = 6825)	eGFR 60 to 89 (ml/min per 1.73 m^2) (n = 7079)	eGFR 15 to 59 (ml/min per 1.73 m^2) (n = 376)
No. of PAD cases	453	516	47
Incidence rate per 1000 person-years	4.7	4.9	8.6
Model 1[a]	1.0	1.04 (0.91 to 1.18)	1.82 (1.34 to 2.47)
Model 2[b]	1.0	1.07 (0.94 to 1.23)	1.56 (1.13 to 2.14)
Model 3[c]	1.0	1.08 (0.94 to 1.24)	1.54 (1.19 to 2.12)
Model 4[d]	1.0	1.10 (0.96 to 1.26)	1.58 (1.14 to 2.17)

[a]Adjusted for age, gender, race, and ARIC field center.
[b]Additionally adjusted for diabetes, LDL and HDL cholesterol, triglycerides, prevalent coronary heart disease, pack-years of cigarette smoking, BMI, physical activity, use of alcohol, and use of cholesterol medication.
[c]Model 2 plus SBP, DBP, and use of antihypertensive medication.
[d]Model 2 plus fibrinogen, factor VII, factor VIII, and white blood cell count.

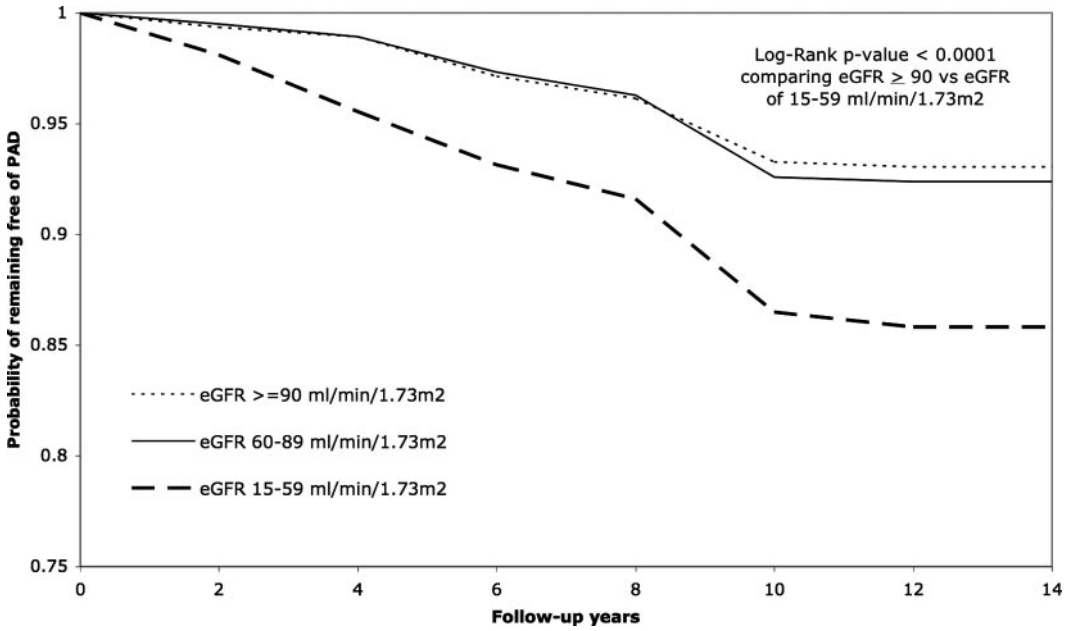

Figure 1. Kaplan-Meier curves for remaining free of peripheral arterial disease (PAD) by level of estimated GFR (eGFR): The Atherosclerosis Risk in Communities (ARIC) Study, 1987 to 2002.

Compared with participants with normal kidney function, the age-, gender-, race-, and ARIC field center–adjusted RR for PAD was 1.04 (95% CI 0.91 to 1.18) for those with mildly decreased kidney function and 1.82 (95% CI 1.34 to 2.47) for those with CKD. After additionally adjusting for CVD risk factors (model 2), an increase in risk for incident PAD still was observed, with multivariable adjusted RR of 1.07 (95% CI 0.94 to 1.23) for those with mildly decreased kidney function and 1.56 (95% CI 1.13 to 2.14) for those with CKD. The multivariable adjusted RR (model 2) for incident PAD is presented in Table 3. Adjusting for covariates in models 3 and 4 did not appreciably alter the RR for PAD in relation to kidney function. Results from the categorical analyses largely were supported by a restricted cubic spline regression, which demonstrated that the multivariable adjusted log hazard of PAD started to increase linearly at eGFR <75 ml/min per 1.73 m^2 (Figure 2).

Formal testing for effect modification showed no statistically significant interaction between any of the variables in Table 1 and the level of kidney function in relation to incident PAD, except for gender (P = 0.02). For men, the multivariable adjusted RR for PAD were 1.00 (95% CI 0.81 to 1.24) for those with mildly decreased kidney function and 2.41 (95% CI 1.53 to 3.80) for those with CKD. For women, the multivariable adjusted RR for PAD were 1.15 (95% CI 0.96 to 1.38) for those with mildly decreased kidney function and 1.19 (95% CI 0.76 to 1.86) for those with CKD.

Table 3. Multivariable adjusted relative risks for incident PAD: The ARIC Study, 1987 to 2002[a]

Variables	Predictors of Incident PAD (RR [95% CI])
Age	1.05 (1.04 to 1.07)
Gender	
female	1.00
male	0.67 (0.56 to 0.80)
Race	
black	1.00
white	0.55 (0.35 to 0.88)
ARIC field center	
Minneapolis	1.00
Washington	2.18 (1.75 to 2.72)
Forsyth	0.99 (0.76 to 1.29)
Jackson	0.88 (0.53 to 1.45)
Diabetes	
no	1.00
yes	1.85 (1.50 to 2.29)
LDL cholesterol	
<100 mg/dl	1.00
100 to 130 mg/dl	1.42 (1.05 to 1.90)
131 to 160 mg/dl	1.46 (1.09 to 1.96)
>160 mg/dl	1.55 (1.15 to 2.08)
HDL cholesterol	
<40 mg/dl	1.00
40 to 60 mg/dl	0.78 (0.65 to 0.94)
>60 mg/dl	0.49 (0.36 to 0.66)
Triglycerides	
<78 mg/dl	1.00
79 to 109 mg/dl	0.93 (0.72 to 1.21)
110 to 156 mg/dl	0.99 (0.77 to 1.28)
>157 mg/dl	0.88 (0.67 to 1.15)
Prevalent coronary heart disease	
no	1.00
yes	2.25 (1.78 to 2.85)
Pack-years of cigarette smoking	
<3.9	1.00
4.0 to 5.4	0.46 (0.36 to 0.59)
5.5 to 7.8	0.46 (0.36 to 0.58)
>7.8	0.88 (0.67 to 1.00)
BMI	
<25	1.00
25 to 30	0.97 (0.80 to 1.18)
>30	0.97 (0.77 to 1.21)
Physical activity	
high	1.00
moderate	1.10 (0.88 to 1.37)
low	1.23 (1.03 to 1.48)
Use of alcohol	
no	1.00
yes	0.90 (0.76 to 1.06)
Use of cholesterol medication	
no	1.00
yes	1.15 (0.79 to 1.69)

[a]CI, confidence interval; RR, relative risk.

Supplemental Analysis

We conducted two supplemental analyses. First, because participants with baseline ABI close to 0.9 might have a greater burden of atherosclerosis, we performed an analysis with additional adjustment for baseline ABI. Adjusted also for the same covariates as listed in the model 2, the RR for PAD was 1.04 (95% CI 0.83 to 1.89) for participants with mildly decreased kidney function and 1.46 (95% CI 0.98 to 2.19) for those with CKD. Second, we also separately examined the associations of CKD with asymptomatic PAD (low ABI <0.9) and symptomatic PAD (intermittent claudication or hospital discharge of PAD-related leg amputation or leg revascularization procedures). Mildly decreased kidney function and CKD were not statistically significantly associated with asymptomatic PAD by low ABI. For symptomatic PAD, having CKD but not mildly decreased kidney function increased the risk for PAD, with a multivariable adjusted RR of 2.28 (95% CI 1.53 to 3.38).

Discussion

We report that individuals with CKD, defined by eGFR between 15 and 59 ml/min per 1.73 m^2, also are at increased risk for developing PAD. Compared with individuals with normal kidney function, the demographic adjusted rate was approximately 80% higher in those with CKD. After adjustment for CVD risk factors, individuals with CKD had a 1.5-fold higher risk for developing PAD than those with normal kidney function.

On the basis of this RR and 4.5% of the US population with CKD (eGFR 15 to 59 ml/min per 1.73 m^2), the population attributable risk for PAD was estimated to be 2.2%. This means that 2.2% of the incidence of PAD in the general population might be attributed to CKD.

The association of CKD with PAD has been examined mostly in cross-sectional studies (6,7,23–25). For example, in NHANES III, individuals with eGFR <60 mg/ml per 1.73 m^2 were more than twice as likely to have prevalent PAD, defined by ABI <0.9, compared with those with eGFR ≥60 mg/ml per 1.73 m^2 (25). This magnitude of association was comparable to that of hypertension, hypercholesterolemia, and a self-reported history of CHD. Nevertheless, prospective studies are needed to understand the temporal relation between CKD and PAD. We are aware of only one other study that specifically evaluated this association longitudinally (9). Using either revascularization procedures or lower extremity amputation as a composite outcome for PAD, the Heart and Estrogen/Progestin Replacement Study (HERS) reported that individuals with eGFR between 30 and 59 ml/min per 1.73 m^2 and individuals with eGFR <30 ml/min per 1.73 m^2 had an increased risk for developing a lower extremity PAD event compared with those with eGFR ≥60 ml/min per 1.73 m^2, with multivariable RR of 1.63 (95% CI 1.04 to 2.54) and 3.24 (95% CI 1.20 to 8.78), respectively. That study derived its cohort from postmenopausal women with documented CHD and did not exclude prevalent PAD at baseline, thus limiting its generalizability and raising questions regarding temporality and reverse causality. Conversely, our cohort was composed of a large, diverse, community-based population of men and women. The HERS and

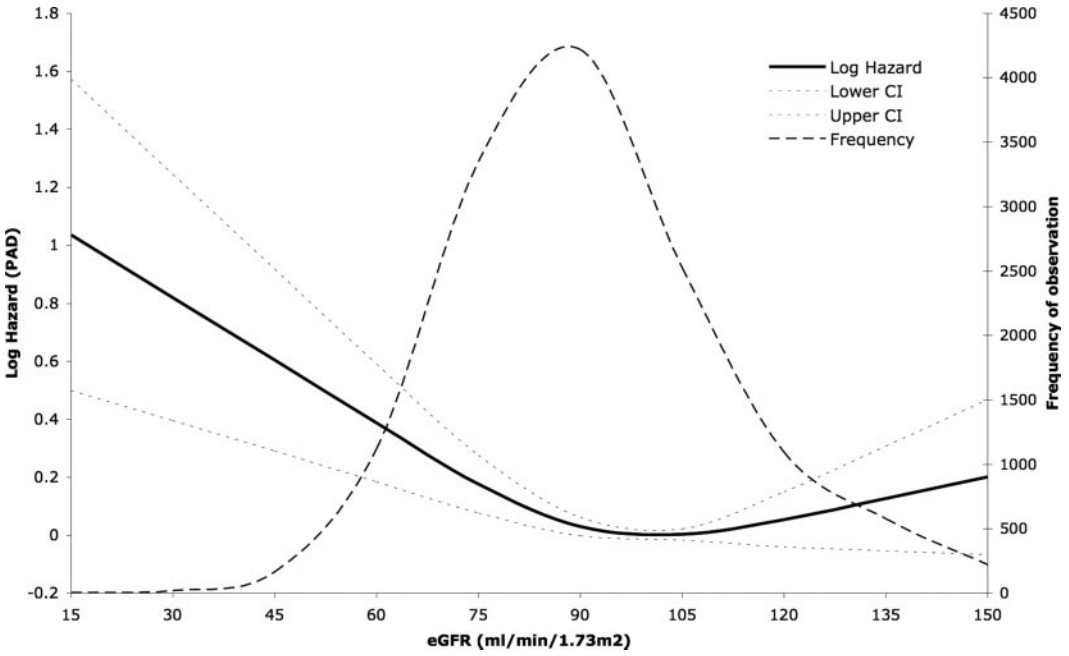

Figure 2. Spline regression of the log hazard of PAD on eGFR: The ARIC Study, adjusted for age, gender, race, ARIC field center, LDL and HDL cholesterol, triglycerides, prevalent coronary heart disease, number of pack-years of cigarette smoking, body mass index, physical activity, use of alcohol, and use of cholesterol medication.

ARIC findings together support the conclusion of previous cross-sectional studies that CKD should be considered a risk marker for PAD.

Possible pathways that link CKD and PAD are unclear. Traditional CVD risk factors, which are highly prevalent in patients with CKD, could contribute etiologically to the development of PAD. In our study, the strength of association was attenuated only modestly after adjustment for traditional CVD risk factors, suggesting that these risk factors may explain only partly an increased risk for PAD in the CKD population. After additional adjustment for SBP and DBP and use of antihypertensive medication (model 3) and inflammatory and procoagulant markers (model 4), the RR for kidney dysfunction essentially were unchanged compared with those in model 2, suggesting that these covariates may not be in a causal pathway that mediates CKD and PAD. Alternatively, the effect of the covariates in models 3 and 4 may be accounted for fully by these traditional CVD risk factors, which are highly prevalent in the CKD population. Other potential pathways that are unique to CKD but that are less well investigated include hyperhomocysteinemia and abnormal calcium and phosphate metabolism. For example, prospective studies have demonstrated that an elevated level of homocysteine is a risk factor for a composite CVD outcome (including PAD) among dialysis-dependent patients with ESRD (26,27). Using a similar study population, Goldsmith *et al.* (28) reported that higher levels of serum phosphate and vitamin D concentrations both were statistically significantly associated with the severity and the rapid progression of vascular calcification, which was hypothesized to lead to arterial stiffness and impaired tissue perfusion.

The findings of our study have clinical implications. Because both CKD and PAD share a number of common risk factors, including hypertension, diabetes, and smoking, it is probable that modification of these risk factors to slow progression of CKD also might beneficially decrease PAD incidence. More important, the findings of our study call for an increased awareness and early detection of PAD in the CKD population. Recognition of an increased risk for PAD in this population, particularly in individuals with no typical ischemic symptoms, potentially could avert adverse limb as well as CVD events if modification of risk factors were intensified. To identify individuals who are at high risk for PAD, the American Diabetes Association recently recommended that a screening ABI be performed in individuals who have diabetes and are older than 50 yr and in individuals who are diabetes and are younger than 50 yr and have other PAD risk factors. Our findings similarly highlight and support development of a PAD screening strategy to identify patients who have CKD and are at high risk for PAD.

This study has several limitations. First, the MDRD formula that was used to estimate GFR was based on individuals with CKD and did not include healthy individuals. Using the MDRD formula in healthy individuals has been shown to underestimate systemically GFR by much as 29% (29). A direct measurement from iothalamate or creatinine clearance using a 24-h urine collection would yield more accurate estimation of renal function. However, direct measurement of GFR is not feasible in a large epidemiologic study. Second, a random sample of participants was invited for the ABI measurements at visits 3 and 4, and these measurements were performed on one posterior tibial artery of a randomly selected leg. This means that we would have missed some participants with asymptomatic PAD.

Furthermore, we would have identified all participants with bilateral PAD and potentially misclassified half of participants with unilateral PAD as non-PAD cases. Hence, the true incidence rate of PAD by low ABI and the magnitude of association with CKD in our study are likely to be underestimated. In addition, this misclassification as a result of ABI measurement of a single leg and inherent measurement error of ABI may explain the null association between CKD and asymptomatic PAD. Third, a few patients who had had amputation and were counted as having PAD may have had amputation for infection. However, the total number of patients with amputations was only 16, so the impact of any misclassification would have been small. Last, C-reactive protein and D-dimer may be important predictors of PAD incidence in the CKD population and unfortunately were not available on the full cohort of the ARIC study cohort.

Conclusion

We found that individuals with CKD are at moderately increased risk for developing PAD. Because early diagnosis of PAD is critical to prevent lower extremity revascularization procedures and amputations, further studies should evaluate whether PAD screening strategies in patients with CKD, particularly those with eGFR <60 ml/min per 1.73 m^2, are effective.

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Disclosures

None.

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