Proteinuria and Risk of Lower-Extremity Amputation in Patients With Peripheral Artery Disease

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Lower-extremity amputation (LEA) is a devastating complication of peripheral artery disease (PAD). Early identification of PAD patients at high risk of LEA is important to enable targeted monitoring and treatment strategies. Although chronic kidney disease is recognized as a high-risk condition for foot complications in diabetes, most previous studies focused on estimated glomerular filtration rate (eGFR). Proteinuria, a marker of kidney damage, has been less studied than eGFR in this context but is a promising predictor of LEA. A small cross-sectional study in the U.K. suggested that albuminuria was associated with foot ulceration in diabetes (1). A recent meta-analysis showed proteinuria as a strong independent predictor of incident PAD and LEA among those without PAD (2). However, whether proteinuria is associated with LEA among patients with diagnosed PAD is unknown. This is an important clinical question since most PAD patients have diabetes or hypertension, two major clinical conditions that merit proteinuria assessment according to clinical guidelines (3,4), and many of them should have data on proteinuria readily available.

Using data from the Geisinger Health System, a fully integrated rural health care system in Pennsylvania (1 March 1997–2 February 2017), we investigated the prospective association between dipstick proteinuria and risk of LEA in a primary cohort of 4,657 patients (2,412 with diabetes) with clinical diagnosis of PAD. Subsequently, we explored urine albumin-creatinine ratio (ACR) in a secondary cohort of 2,506 patients with PAD and diabetes. The exposure was defined as the closest outpatient dipstick proteinuria and ACR within 2 years prior to the baseline date (i.e., the first recorded date of PAD diagnosis) for the primary and secondary cohorts, respectively. LEA was determined by ICD codes (84.1x, Z89.4x, Z89.5x, Z89.6x, and 0Y6x). We used Cox proportional hazards regression models and adjusted for age, sex, race, baseline year, smoking, hypertension, cardiovascular disease, medication use, eGFR, duration of diabetes, diabetic retinopathy, and diabetic neuropathy. We further adjusted for hemoglobin A_{1c} (HbA_{1c}) in the analysis of the secondary cohort of patients with diabetes. We estimated the difference in Harrell C-statistics between prediction models that included or excluded dipstick proteinuria/ACR. This study was reviewed and approved by the Geisinger and Johns Hopkins University institutional review boards.

The mean baseline age of 4,657 individuals in the primary cohort was 69.5 (SD 12.9) years, 45% were women, 52% had diabetes, and mean eGFR was 63.7 (SD 29.2) mL/min/1.73 m^2. The 5-year incidence of LEA was 7% for dipstick protein negative, 9% for trace, 13% for 1+, and 21% for ≥2+. This dose-response relationship remained significant even after accounting for potential confounders (P_{trend} <0.001), with an adjusted hazard ratio (HR) of 1.44 (95% CI 1.10–1.88) for 1+ and 1.70 (95% CI 1.32–2.19) for ≥2+, compared with negative (Table 1). The addition of dipstick proteinuria slightly but significantly improved LEA risk discrimination (Δ in the C-statistic = 0.008 [95% CI 0.001–0.014] from 0.714 with the base model with all covariates).

Among 2,506 individuals with PAD and diabetes in the secondary cohort, mean age at baseline was 69.2 (SD 11.2) years, 39% were women, mean HbA_{1c} was 7.5% (SD 1.6%), and mean eGFR was 66.5 (SD 26.3) mL/min/1.73 m^2. Results in the secondary cohort were consistent with the primary analysis, with an adjusted HR of 1.50 (95% CI 1.07–2.09) for ACR 30–300 mg/g and 1.61 (95% CI 1.07–2.43) for ACR >300 mg/g, compared with ACR <10 mg/g (P_{trend} = 0.02) (Table 1). Notably, even ACR 10–29 mg/g

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Table 1—Adjusted HR (95% CI) of LEA associated with dipstick proteinuria and ACR

Exposure	Events/*N*	Person-years	HR (95% CI)		
Primary cohort: analysis among patients with PAD (N = 4,657); median follow-up 3.5 years (IQI 1.1–6.9 years)					
Dipstick proteinuria category			Model 1	Model 2	Model 3
Negative	192/2,596	12,781	Reference	Reference	Reference
Trace	56/539	2,592	1.38 (1.03–1.87)	1.42 (1.05–1.92)	1.32 (0.97–1.78)
1+	77/660	2,553	1.74 (1.34–2.27)	1.61 (1.23–2.11)	1.44 (1.10–1.88)
≥2+	140/862	2,669	2.70 (2.17–3.37)	2.18 (1.69–2.80)	1.70 (1.32–2.19)
P_{trend}			<0.001	<0.001	<0.001
Secondary cohort: analysis among patients with PAD and diabetes (N = 2,506); median follow-up 4.3 years (IQI 1.6–7.1 years)					
ACR, mg/g			Model 1	Model 2	Model 3
ACR <10	47/647	3,674	Reference	Reference	Reference
ACR 10–29	76/604	2,942	1.78 (1.25–2.54)	1.74 (1.22–2.49)	1.47 (1.03–2.11)
ACR 30–300	113/881	3,859	1.96 (1.41–2.71)	1.82 (1.32–2.54)	1.50 (1.07–2.09)
ACR >300	59/374	1,352	2.56 (1.77–3.72)	2.14 (1.43–3.19)	1.61 (1.07–2.43)
P_{trend}			<0.001	<0.001	0.02

Model 1: adjusted for age, sex, and race. Model 2: Model 1 adjustments + baseline year, smoking, hypertension, cardiovascular disease (coronary artery disease, heart failure, or stroke), medication use (renin-angiotensin system inhibitors, antiplatelets, and statins), and eGFR. Model 3: Model 2 adjustments + duration of diabetes, diabetic retinopathy, diabetic neuropathy, and HbA_{1c} (secondary cohort only). IQI, interquartile interval.

showed significant associations with LEA (HR 1.47 [95% CI 1.03–2.11]). Again, LEA risk discrimination was significantly improved by adding ACR to the base model with all covariates (Δ in the C-statistic = 0.015 (95% CI 0.004–0.026) from 0.678). We observed similar results in rigorous sensitivity analyses, including competing risk models and different definitions of exposure (e.g., the highest dipstick proteinuria value within 2 years prior to the baseline date and a 2-year average of ACR).

Our study showed that proteinuria was robustly associated with future risk of LEA in PAD patients, independent of eGFR. Proteinuria significantly improved risk discrimination of LEA beyond demographic and other clinical factors. The American Diabetes Association recommends an annual foot evaluation for patients with diabetes (3), but the adherence to this recommendation is still suboptimal (5). Our results indicate that providers should be particularly cognizant of PAD patients with diabetes with elevated proteinuria and encourage annual foot monitoring and optimal PAD management. As the evaluation of proteinuria is already recommended in some clinical conditions such as diabetes, it is important that health care providers pay attention to its value, when available, in risk assessment of limb loss in patients with PAD.

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