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Subclinical peripheral arterial disease in patients with chronic kidney disease: Prevalence and related risk factors

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Background. Atherosclerotic artery disease is a common condition in patients with chronic kidney disease (CKD); however, there are few published data on the prevalence of peripheral arterial disease (PAD) in nondialyzed patients with renal insufficiency. The ankle-brachial index (ABI) is a simple, noninvasive, and reliable method to assess PAD.

Methods and Results. Prevalence of PAD using ABI was investigated in 102 patients referred for the first time to a nephrology clinic with CKD in stages 3 to 5 of the K/DOQI classification, and with no previous diagnosis of PAD. Patients with ABI <0.9 were considered positive for PAD.

A total of 64% of the patients were male. The mean age was 70 ± 11 (range 58–84) years, and the estimated creatinine clearance (CrCl) was 35 ± 12 (range 6–59) mL/min^{-1}. Of the total sample, 26% were diabetics, 10% active smokers, 48% ex-smokers, and 29% had a diagnosis of coronary heart disease (CHD), 15% had been previously diagnosed of stroke, and 17% had signs and symptoms compatible with intermittent claudication, which had passed unnoticed. Thirty-two percent of patients had an ABI <0.9 (mean 0.64 ± 0.25). Of these patients with PAD, 84% were men ($P < 0.005$), and only 30% presented a clinical picture compatible with intermittent claudication. Absolute risk of CHD according to the Framingham 1998 score was higher in the PAD group (19.3% ± 6 vs. 13.1% ± 8; $P = 0.01$). Patients with PAD were older (75 ± 6 vs. 66 ± 11 years, $P = 0.000$), and had worse renal function (CrCl 30.8 ± 12 vs. 37 ± 10.7 mL.min^{-1}, $P = 0.016$) compared to patients without PAD, but no differences were found in cholesterol levels (total, HDL, LDL), calcium, phosphorus, or PTH. In the logistic regression analysis, independent indicators of PAD risk were male sex, age, and lower CrCl.

Twelve percent of patients had an ABI ≥1.3, suggestive of parietal arterial calcifications. In these patients, systolic blood pressure and pulse pressure were lower (126 ± 18 vs. 150 ± 27, $P = 0.005$, and 52 ± 13 vs. 68 ± 25 mm Hg, $P = 0.044$), i-PTH levels were higher (228 ± 267 vs. 117 ± 63 pg/mL, $P = 0.01$), and a larger proportion of this group was treated with calcitriol (34% vs. 13%) compared to patients with a normal ABI.

Conclusion. A high prevalence of PAD, considered as an ABI <0.9, was demonstrated in nondialyzed patients with CKD. This was related with age, male sex, and higher degree of renal insufficiency, while the presence of ABI ≥1.3 was associated with a greater degree of hyperparathyroidism. These data show the need to carry out routine ABI determinations in patients with CKD for early detection of peripheral arterial disease.

Key words: peripheral arterial disease, chronic kidney disease, cardiovascular risk, ankle brachial index.

Patients with chronic kidney disease (CKD) are highly predisposed for developing accelerated atherosclerosis, even in the absence of certain traditional cardiovascular risk factors [1]. Moreover, frequently these patients not only present traditional risk factors such as hypertension, diabetes, or dyslipidemia, but also other nontraditional factors such as inflammation, malnutrition, and oxidative stress, which enhance and accelerate atherosclerosis. Minor renal dysfunction influences cardiovascular risk [2–5]. Although the relationship between myocardial infarction, stroke, and cardiovascular death with renal dysfunction is well established, there are few data on the prevalence of peripheral arterial disease (PAD) in the lower extremities in patients with CKD. PAD is associated with high mortality, 3 times higher than that of the general population [6], even in patients without CKD, and its prevalence appears to be much higher among end-stage renal disease patients, as evidenced by the high amputation rates in this group compared to the general population [7]. However, it has not been as extensively studied as other atherosclerotic diseases, such as coronary artery disease and cerebrovascular disease, and there are few data about its prevalence in earlier stages of CKD. A recently published study based on data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000 on PAD in individuals with renal insufficiency using the ankle-brachial index (ABI) confirmed the high prevalence of PAD, defined by an ABI <0.9, among patients with renal insufficiency in nonadvanced stages (CrCl <60 mL/min^{-1}/1.73m^{-2}), independent of patient's age, diabetes, coronary disease, stroke history, and hypercholesterolemia. This implies that routine use of ABI measurements in these patients would greatly increase detection of subclinical PAD [8].

ABI is a noninvasive diagnostic test that is easy to perform, reproducible, and efficient in detecting subclinical PAD. It has also been shown to be a strong predictor of cardiovascular disease and of mortality. An ABI <0.9 is 95% sensitive and 100% specific for angiographically documented PAD for arterial stenosis ≥50% in the lower extremities [9, 10].

In the present work, we investigated the prevalence and risk factors associated with subclinical PAD in nondialyzed patients with CKD with varying degrees of renal insufficiency using the ABI.

Table 1. Patient characteristics

No. of patients	102
Sex % *males*	64%
Age *years*	70 ± 11
SBP *mm Hg*	148 ± 23
DBP *mm Hg*	79 ± 12
PP *mm Hg*	68 ± 19
Diabetes %	26
Smokers %	10
Dyslipidemia % *treated with statins*	47
Coronary heart disease %	29
Cerebrovascular disease %	15
Antiplatelet therapy %	45
Calcitriol treatment %	14%
BMI kg/m^{-2}	29 ± 11

METHODS

This study was done between October 2003 and April 2004 in adult patients referred for the first time to the nephrology outpatient clinic. We included 102 patients of both sexes with stages 3 to 5 of CKD (K/DOQI) not previously diagnosed with PAD, defined as an atherosclerotic disease that causes ischemia in the legs, confirmed by arteriography, vascular Doppler, or treated with surgery, stent, or amputations. All patients had CrCl <60 mL/min^{-1} calculated using the Cockroft-Gault formula [11] and were hypertensive receiving drug therapy, 47% had dyslipidemia treated with statins, and 45% received antiplatelet treatment. Patients on dialysis, renal transplants, or with an arteriovenous fistula were all excluded. The renal disease had a vascular etiology in 24%, diabetic nephropathy in 16%, unknown in 26%, chronic interstitial nephropathy in 13%, and was associated with other causes in the remaining 21%.

Twenty-six percent of patients had type 2 diabetes, 29% had coronary heart disease confirmed by coronariography, a previous myocardial infarction, or surgery or coronary revascularization, and another 15% had cerebrovascular disease with a clinical history of stroke with neurologic deficit, or confirmed by arteriography, computerized tomography, magnetic resonance, or surgical treatment/stent of the carotid arteries.

Patients were considered to be active smokers if they had smoked at all during the last month; ex-smokers if they had ever smoked; and nonsmokers if they had never smoked.

For all patients, the ABI was calculated using a portable pulse detector (Ultrasonic Mini Doppler ES-100; Hadeco, Inc., Arima, Japan) and an 8 mHz probe. Systolic blood pressure (SBP) measurements were taken in both arms and legs after 5 minutes at rest in decubitus supine. The ABI was calculated for each leg on the basis of the SBP of the arm where this was highest and according to the formula:

SBP in posterior tibial artery or dorsalis pedis artery/brachial SBP

An ABI ≥0.9 and <1.3 in both legs was considered as normal, and patients were diagnosed as having PAD if the value recorded for one of the legs was <0.9 or ≥1.3.

In all patients, absolute risk of coronary heart disease within the next 10 years was calculated based on Framingham's score for men and women [12].

Table 1 shows the characteristics of the patients included in the study.

Statistic methodology

Data are expressed as mean ± SD. All statistic analysis was performed using a computerized statistical package (SPSS for Windows, version 11.01; SPSS, Inc., Chicago, IL, USA). Chi-square test was used for qualitative variables, and Student *t* test was used to analyze differences in the continuous variables between pathologic and normal ABI. Finally, multiple logistic regression analysis was done.

RESULTS

Fifty-seven patients (56%) had a normal ABI, 33 (32%) had an ABI <0.9, and 12 (12%) an ABI ≥1.3. The differences between patients with a normal and a pathologic ABI are shown in Table 2.

Patients with an ABI <0.9 were mainly older, male, ex-smokers with a worse renal function, and lower DBP measurements. Calculation of the absolute risk of coronary disease in the following 10 years revealed a high risk of near 20%. Of these patients with an ABI <0.9, only 30% had signs and symptoms compatible with intermittent claudication, defined as pain on walking that disappeared when resting, and all others were asymptomatic. None referred to pain while resting. Multiple logistic regression analysis demonstrated that the risk factors for an ABI <0.9 were older age, male sex, and a lower CrCl (Table 3).

Twelve percent of patients had an ABI ≥1.3. These patients were usually diabetics, had higher LDL-cholesterol levels, and lower blood pressure levels, but there were