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Peripheral arterial disease in haemodialysis patients: prevalence and risk factors

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ABSTRACT

Background: Haemodialysis patients are at increased risk of progressive peripheral arterial disease. The rate of peripheral arterial disease is not well defined, due to a lack of standard disease definition and recognition. The aim of this study is to establish the prevalence of peripheral arterial disease and to identify the associated risk factors.

Methods: We included 109 haemodialysis patients from two centres in a cross-sectional study. Mean age of patients was 59.1 ± 14.8 years, and 23% had diabetes. Patients underwent echo Doppler. Arterial vascular characteristics (thickness, calcification, presence of atherosclerotic plaques), flow wave and ankle-brachial index in lower extremity arterial Doppler were determined. The definition of occlusive peripheral arterial disease required an ankle-brachial index value ‹ 0.9 or monophasic flow wave. The presence of claudication was determined by a questionnaire. Echo Doppler findings were analysed in relation to gender, age, diabetes mellitus, hypertension, the mean time on dialysis, total low-density lipoprotein and high-density lipoprotein cholesterol levels, calcium, and phosphorus levels, intact parathyroid hormone level, albumin level and C reactive protein level.

Results: Atherosclerotic plaques were found in 49.9%. In 71.4%, peripheral arterial disease was femoropopliteal and bilateral in 81.6%. Occlusive peripheral arterial disease was present in 16.9%. All patients with peripheral arterial disease had media calcification. In addition, 32.1% patients had media arterial calcification without signs of peripheral arterial disease. Peripheral arterial disease was associated with older age, longer mean time on dialysis, higher low-density lipoprotein cholesterol levels and lower levels of serum calcium. Claudication was present in 14 patients with peripheral arterial disease, 7 patients with media arterial calcification and 4 patients with no vessel lesions.

Conclusions: Clinicians should be aware of the remarkably high prevalence and severity of peripheral arterial disease among haemodialysis patients. Claudication is a poor indicator of peripheral arterial disease. Echo Doppler is a non invasive method which appears to be efficient in detecting peripheral arterial disease. Ankle-brachial index measurement and flow wave could be of use in identifying patients with sub clinical occlusive peripheral arterial disease. Future studies are needed to clarify the risk factors and to establish preventive measures.

Key-Words:
Haemodialysis; peripheral arterial disease; risk factors.

INTRODUCTION

Peripheral arterial disease (PAD) is very common in chronic kidney disease (CKD) patients, leading to significant mortality and morbidity[1]. Depending on the population studied and the diagnostic tools used, the rate varies from 17-48%, significantly higher than in the gen-

eral population[1-4] although here it seems to be on the increase. In an abstract published in 1990, the prevalence of PAD in CKD patients undergoing dialysis 1983-1987 was 60%, twice as high as the rate found in 1976 and 1982[5]. In the Medicare System, a retrospective study published in 1999 demonstrated that 6.2 % of dialysis population was submitted to non-traumatic amputation of lower limbs in 1994 and 2/3 of these patients died within two years. In 1991, the percentage of patients submitted to lower limb amputation was significantly lower (4.8%)[1] than in 1999.

The prevalence of PAD varies with the study population and the diagnostic methods used[2]. For epidemiological purposes, the most commonly used non-invasive method is ankle-brachial Index (ABI) measured using Doppler techniques. Resting ABI level of 0.90 has been suggested to be 95% sensitive in detecting angiogram-positive PAD and almost 100% specific in identifying disease in apparently healthy individuals. In dialysis population, falsely elevated pressures are common due to vascular calcifications[6]. Arterial intimae calcification (AIC) represents an advanced stage of atherosclerosis and is associated with the development of plaques and occlusive lesions[7]. However, medial arterial calcification (MAC) or Monckeberg´s arteriosclerosis may be also observed and predominantly affect muscle-type conduit arteries. It remains a subject of controversy if MAC, a common finding in dialysis and diabetes patients, is associated with adverse cardiovascular outcomes[8].

The aims of this study were to determine the prevalence of PAD in CKD patients undergoing regular dialysis, to establish the risks factors associated with the development of PAD and to characterise arterial calcifications in this population. We have used echo Doppler, as this non invasive method identifies the presence of atherosclerotic plaques and arterial calcifications, either localised to intimae or/and to media. In addition, ABI and flow wave were registered in order to establish the diagnosis of occlusive PAD.

PATIENTS AND METHODS

Study design

Our study is a cross–sectional double-centre study of CKD patients on haemodialysis (HD), performed between January 2003 and March 2004.

Population

One hundred and nine CKD patients on HD for at least three months (4-240 months), 53.2% male and 21.1% diabetic. Patients who had been submitted to previous lower extremity amputation or surgical revascularisations were excluded, as they could not undergo Doppler analysis.

Patients were dialysed with synthetic high flux membranes and bicarbonate dialysate with 1.5mmol/L calcium. 1.25-dihydroxy vitamin D3 was used to control the parathyroid hormone (PTH) levels. Calcium carbonate was used to try to maintain pre-dialysis serum phosphate ‹ 5.5 mg/dl and pre-dialysis serum calcium› 8 mg/dl.

All patients underwent lower extremity Doppler analysis (Vivid 7) to identify the presence of atherosclerotic plaques and arterial calcifications. Two experienced clinicians made these measurements blindly. Arterial calcification was classified as intimal plaques or uniform medial calcification by identifying double contour, corresponding to the *rail-road sign* on the radiogram technique. The flow wave was registered, with a triphasic flow wave considered normal. Both femoral arteries, from external iliac to 5 cm of superficial femoral artery, origin of profound femoral and popliteal arteries were studied. The arterial vascular characteristics (thickness, calcification, presence of atherosclerotic plaques) were registered and the flow wave was determined in the least calcified site of the femoral and popliteal arteries.

The ABI was determined by measuring the systolic blood pressure in the pediosa and posterior tibial arteries after resting 15 minutes with the study subject in supine position. This value was divided by the brachial systolic blood pressure from the arm free of the shunt. The lowest value for each patient was considered for analysis.

Haemodynamic repercussion was considered to be present if the flow wave was monophasic or ABI‹ 0.9.

According to the Doppler results, three groups were established considering the lower limb with the most severe lesions:

Group I- Without morphological lesions or haemodynamic alterations.

Group II- Double contour in the arterial wall and absence of intimal atherosclerotic plaques.

Group III- Double contour in the arterial wall and presence of intimal atherosclerotic plaques.

Hypertension was diagnosed when a study subject had received medical treatment for hypertension or had a systolic blood pressure of 140 mmHg or diastolic blood pressure of 90 mmHg at the time of examination. Diabetes was considered if there was a documented history of the disease. Smokers, non-smokers, and ex-smokers were identified.

Criteria for concomitant coronary artery disease (CAD) included a history of documented myocardial infarction, the presence of a positive stress test, a coronary angiogram showing significant occlusive disease, history of typical angina pectoris or coronary bypass surgery. The definition of cerebral vascular disease (CVD) included a history of documented stroke or transient ischaemic attack. Evaluation of carotids by Doppler was not available.

The presence of claudication was defined as exercise calf pain not present at rest and relieved within 10 minutes by rest (according to the WHO/Rose questionnaire)[9].

Pre-dialysis serum calcium, phosphorus, C-reactive protein (CRP) was determined every month. Serum albumin, blood lipids, and iPTH were measured every 3 months. The values considered in the present study are the averages of all above mentioned measurements over the 1 year period preceding the study.

Statistical Analysis

Data are expressed as mean ± SD or as %, and for comparison between groups, Student t and chi-square test were performed. P value less than 0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 59.1 ± 14.8 years (22-88 years), and the mean duration of dialysis treatment was 61.3 ± 50.7 months (4-240 months). There were 58 female patients (53.2%). Twenty-three percent of patients were diabetic, 79.8% had hypertension and 23.9% were smokers. In 28.7% of patients, the total serum cholesterol was › 200 mg/dl and 11. 5% had LDL-cholesterol › 160 mg/dl.

The causes of renal failure in the 109 patients included hypertension in 33 and diabetes mellitus in 16 patients.

Twenty-five patients met the Doppler criteria for Group I (22.9%), 35 for Group II (32.1%) and 49 for Group III (49.9%). Thus, the prevalence of atherosclerotic plaques on peripheral arteries was 49.9% and MAC was found in 32.1%. All patients from Group III also presented medial calcification (Table I).

Table I

Clinical characteristics of the patients

	Group I (n=25) (No lesions)	Group II (n=35) (Medial calcifications)	Group III (n=49) (Atherosclerotic plaques)
Age (Y)	**49.3 17.1**	**59.7 14.2***	**63.6 11.1****
Gender (M/F)	8/17	18/17	32/17
Race (B/W)	9/16	7/28	4/45
Months on dialysis	**36.6 29.9**	**62.9 54.9****	**70.5 54.4****
Claudication (Y/N)	4/21	7/28	14/35
Smokers (Y/N)	4/21	10/25	12/37
Hypertensive patients (Y/N)	22/3	29/6	36/13
Diabetic patients (Y/N)	4/21	7/28	12/37
Concomitant CAD (%)	**0**	**12**	**46.9****
Concomitant CVD (%)	**0**	**3.4**	**14.2***

Patients from two haemodialysis centers were submitted to Doppler analysis by two experienced clinicians, blindly. Type of flow and ABI was determined. Statistical analysis were performed with Student t-test (age and months on dialysis) and with chi-square test (for the other variables). Statistical significant, when p ‹0.05; *p‹0.05; **p‹0.001

Anatomical atherosclerotic plaques distribution was the following: femoro-popliteal atherosclerotic plaques were present in 35 patients (71.4%), femoral distribution in 5 patients and popliteal distribution in 9 patients. Atherosclerotic plaques were bilateral in 40 patients (81.6%).

On 18/49 patients (16.5% of 109 patients), atherosclerotic plaques were considered to be occlusive. Ten patients (9.2% of 109 patients) had proximal arterial disease.

Claudication was present in 22.9% patients; 4 in Group I, 7 in Group II, and 14 in Group III. In Group III, 5/14 patients had occlusive PAD.

Patients of Group II and III were significantly older than those in Group I and had been undergoing dialysis longer (p<0.001). The subgroup with occlusive disease had mean age of 65.1 ± 12.1 years (compared to 62.7 ± 10.6 years in the others) and mean time on dialysis 67.52 ± 55.6 months (64.7 ± 49.5 months in the others) (Table I).

Twenty-two patients had hypertension in Group I (88%) *versus* 29 patients in Group II (82.9%) *versus* 36 patients in Group III (73. 5%). Four patients were diabetic in Group I (16%) *versus* 7 patients in Group II (20%) *versus* 12 patients in Group III (24.5%) (Table I). These differences had no statistical significance.

Numbers of smokers, nonsmokers, and ex-smokers were similar between the three groups.

Group III was significantly associated with CAD (p<0.001) and CVD (p<0.01) (Table I). Concomitant CAD was present in 23 Group III patients (46.9%) *versus* Group II 3 patients (12%). In Group III, 13.9% of the patients had already undergone coronary bypass surgery. Concomitant CVD was present in 6 Group III patients (14.2%) *versus* 2 Group II patients (3.4%). There was no history of CAD or CVD in Group I (Table I).

Serum calcium concentration tended to be higher and the calcium-phosphorus ion product in serum was higher in Groups I (Ca x P=47.3 ± 12.1, Ca=9.2 ± 0.7 mg/dl) and II (Ca x P=45.6 ± 15.5, Ca=9.3 ± 0.6 mg/dl) compared with Group III (Ca x P=41.5 ± 12, Ca=8.9 ± 0.7 mg/dl) not statistically significant, however (Table II).

Table II

Biochemical findings

	Group I (n=25) (No lesions)	Group II (n=35) (Medial calcifications)	Group III (n=49) (Atherosclerotic plaques)
LDL-cholesterol (mg/dl)	**89±31.4**	**89±36.7**	**116±33.7***
HDL -cholesterol (mg/dl)	49.4±18.2	43.8±7.9	47.1±12.9
Triglycerides (mg/dl)	146±53.3	126±45	187.5±91
iPTH (pg/ml)	222.1±200.1	207.0±186.4	182.8±175.2
Ca x P (mg/dl)2	**47.3±12.1**	**45.6±15.5**	**41.5±12.0***
Ca (mg/dl)	**9.2±0.7**	**9.3±0.6**	**8.9±0.7***
P (mg/dl)	5.0±1.2	4.9±1.5	4.7±1.3
Albumin g/L	3.7±0.3	3.5±0.2	3.5±0.3
CRP (mg/l)	0.7±0.3	1.0±0.9	0.8±0.5

Data are mean SD, and the averages of all measurements obtained over the 1 year preceding the study; non paired t- test was used for statistical analysis. Statistical significant, when p <0.05 (*p<0.05).

Relative to lipid profile, low density lipoprotein (LDL) cholesterol levels were significantly higher in Group III than in Group I and II. Serum high density lipoprotein (HDL) cholesterol and triglycerides did not differ significantly between the three groups. Group II and III had significantly higher levels of total cholesterol than Group I (Table II).

DISCUSSION

The prevalence of PAD on haemodialysis patients is not clearly established. In a review made by O´Hare and Johansen, the prevalence varied between 2.4 and 46%, based on clinical criteria (amputation, claudication, gangrene and reduced pulses)[2]. The utilisation of non-invasive diagnostic techniques demonstrates prevalence from 16.6 to 38.3%[2,5]. Thus, it appears that PAD is highly prevalent in the dialysis population.

In this study, as we chose to perform Doppler analysis on all patients from two dialysis centres, looking for peripheral arterial disease, we therefore decided not to include 3 patients who had undergone prior amputation. Atherosclerotic plaques were present on 49.9% of 109 patients on haemodialysis. In the majority of the patients, the disease was bilateral (on 40 of these patients, 81.6%) and femoro-popliteal (35 patients, 71.4%). Of note, 36.7% of these patients (18/49 patients, 16.5% of 109 patients) had occlusive disease. All of these patients showed calcification in the media and in the intimal plaques. Additionally, we also found isolated medial calcification in 32.1% patients. In comparison, Leskinen *et al* found a higher prevalence of occlusive PAD, as 30.6% patients had an ABI ≤ 0.9%[10]. DOPPS demonstrated that PAD was diagnosed in 25% patients[11]. Guerrero *et al* found occlusive PAD in 19% of patients with stages IV and V chronic renal failure[12].

ABI values can be falsely elevated among patients with lower-extremity vascular calcification as calcified arteries tend to be incompressible[10]. Thus, it is likely that estimation of the prevalence of PAD that is based on ABI testing underestimates the true prevalence of PAD in the CKD population. Therefore, we decided to register the flow wave determined in the least calcified site of the femoral and popliteal arteries.

Twenty two percent of patients had claudication, a surprising low prevalence compared to a remarkably high prevalence of PAD, meaning claudication seems to be an insensitive indicator of PAD. It may be that older people tend to have reduced physical activity and are accordingly less symptomatic. In Group I and II, 4 patients and 7 patients were symptomatic *versus* 14 patients in Group III. Interestingly, Leskinen *et al* demonstrated that 30% of dialysis patients with claudication did not have occlusive arterial disease according to ABI[10]. Furthermore, in the general population, an important proportion of patients with claudication did not show arterial disease of proximal vessels[13].

Cardiovascular morbidity and mortality are highly prevalent in HD patients. Our study showed coronary artery disease in 58.9% patients and cerebrovascular disease in 15.4%. Patients with PAD showed 46.9% and 12% respectively, as opposed to 12% and 3.4% in patients with MAC. Other studies have shown that a low ABI is a predictor of cardiovascular mortality, working independently from other risk factors of mortality[12,14].

The higher prevalence of atherosclerotic disease in CKD patients may be explained by a higher frequency of traditional risk factors such as hypertension and diabetes among these patients. Renal failure can also be a marker of or be associated with accelerated atherosclerosis, as uraemia is an oxidative state. Moreover, several unconventional cardiac risk factors, such as hyperparathyroidism, lipoprotein (a) levels, hyperhomocysteine and chronic inflammation, may play significant roles in the development or progression of PAD in HD patients[15].

Some investigators have tried to identify the risk factors associated with peripheral arterial disease. In a multivariate analysis of 1000 haemodialysis patients, Cheung *et al* observed a statistically significant association between PAD and age, cigarette smoking, diabetes and non-Caucasians[15]. DOPPS demonstrated that traditional cardiovascular risk factors, including age, male sex, diabetes, hypertension, and smoking were positively associated with PAD as well as the duration of haemodialysis[11]. In our study, age, length of time on dialysis therapy and LDL cholesterol were correlated with PAD. In fact, we found higher LDL-cholesterol levels in Group III, despite the value being in the normal range recommended and no other lipid abnormalities being identified as a risk factor for PAD. It is possible that lipids levels might reflect a chronic state of malnutrition[9] or that the lipid value obtained in this study as the mean of four determinations does not reveal the severity and duration of dyslipidemia in these patients. On the other hand, it might be that the vessel wall in these patients is more sensitive to lipid. At present, a high-risk strategy approach, aiming at a lower lipid serum levels, has not been recommended.

High calcium, secondary hyperparathyroidism and hyperphosphataemia have been associated with vascular calcification[10,16,17]. In this study, we found higher levels of calcium in Group I and II than in Group III, and no difference in phosphate and PTH levels between the groups. It is not completely proven that higher levels of calcium cause vascular calcification[15,18]. Some authors have suggested that another factor might exist and modify the calcification process, such as the deposit of bone matrix proteins in the vessel wall[18]. It is noteworthy that as we have only analysed the mean of the preceding 12 months values, those values might not represent the values preceding the onset of vessel calcification[20].

A limitation of this study is the qualitative evaluation of the calcifications. Intimal and medial forms are usually distinguished easily with good interobserver concordance, but the intensity of calcification in terms of the quantitative calcium per gram cannot be determined with this technique. Some authors have suggested that atherosclerotic plaques calcification may be more intense in dialysis patients[21].

Early identification of PAD before the progression to advanced ischemia is particularly important in dialysis patients, since the outcomes are extremely poor and poor survival rates are found after amputation. Surgical revascularisation is not routinely offered because these patients often heal poorly, have high rates of wound infections and the patency of bypass graft is poor[4].

It is probable that effective screening would allow us to identify patients likely to benefit from PAD-specific educational interventions and therapy which are of proven value in the treatment of noncritical ischemia[22,23].

In conclusion, PAD is highly prevalent in dialysis patients and asymptomatic disease is common in this population. The disease tends to be bilateral and femoro-popliteal. Doppler analysis may be used to identify PAD as claudication seems to be a poor indicator. Occlusive disease can be recognised by ABI or monophasic pressure wave. Future studies are required to clarify risks factors and to establish preventive therapies.

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Conflict of interest statement. None declared.

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