Modern Medicine. 2015, Vol. 22, No. 4 : 359-365

Review

Peripheral Arterial Disease in Hemodialysed Patients

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REZUMAT

Arteriopatia obliterantă la pacienții hemodializați

Recent s-a evidențiat faptul că arteriopatia obliterantă este des observată la populația hemodializată, în special la pacienții fumători și cunoscuți cu diabet zaharat. Având în vedere prevalența ridicată de bolnavi dializați la nivel mondial, în articolul de față prezentăm două cazuri particulare de hemodializați cronic cu diagnostic pozitiv de arteriopatie obliterantă, la care lipsesc anumiți factorii de risc obișnuiți responsabili de apariția și progresia acestei afecțiuni. Pentru o mai bună înțelegere a mecanismelor fiziopatologice incriminate, dar și a rolului stresului oxidativ și inflamației cronice în dezvoltarea și evoluția acestei patologii, este nevoie de derularea de ample studii clinice și experimentale.

Cuvinte cheie: arteriopatia obliterantă, stresul oxidativ, inflamația cronică, hemodializa, prognostic

ABSTRACT

Nowadays, peripheral artery disease (PAD) is often emphasized in hemodialysed population, especially in patients associating diabetes mellitus and a long-term tobacco addiction. Considering the worldwide high prevalence of dialysed individuals, we present two particular cases of chronic hemodialysed patients diagnosed with peripheral artery disease, even in the absence of usually incriminated risk factors. Our report highlights that the underlying conditions responsible for PAD development and progression are far from being entirely comprehended and further clinical and experimental trials are required to a better understanding of the pathophysiological mechanisms and the role of oxidative stress and chronic inflammation in the onset of this disorder.

Key words: peripheral artery disease, oxidative stress, chronic inflammation, hemodialysis, outcome

INTRODUCTION

There is increased evidence that the prevalence of peripheral artery disease (PAD) in hemodialysed patients is higher than in general population [1,2]. According to ACC/AHA (American College of Cardiology / American

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Heart Association) guidelines, the following risk factors are associated with PAD [3,4]:

- male gender;
- age over 70 years or > 40 in diabetic and/or smokers patients;
- smoking;
- diabetes mellitus;
- atherosclerosis (personal and/or family history);
- dyslipidemia;
- systemic hypertension;
- hyperhomocysteinemia;
- presence of intermittent claudication, ischemic pain at rest, non-healing ulceration or gangrene;
- decreased pulse of lower limbs.

Additionally, the diagnosis is confirmed when an ankle-brachial index below 0.9 is emphasized correlated with abnormal physiologic (e.g.: segmental pressures, pulse volume recordings) and/or vascular imaging tests (e.g.: duplex ultrasound, arteriography) [3,5].

Over the years, considering the increased oxidative stress and inflammatory state linked to this disease, among other incriminated pathophysiological mechanisms, several therapeutically options have been proposed in order to slow PAD progression – antichlamydia treatment [6-9], antioxidants [10-15], phosphodiesterase inhibitors [16-21], prostanoids [22-32], angiotensin-converting enzyme inhibitors [33-39] or endothelin-1 receptor antagonist [40-44] administration, hemodilution [45-50], immune modulation [51-58], stem cells [59-64] or hyperbaric oxygen therapy etc; although consistent progresses have been made, percutaneous or surgical revascularization still remains the gold standard treatment [65].

As previously highlighted, PAD is often diagnosed in dialysed patients, especially in chronic hemodialysed population, probably due to various associated risk factors related to chronic kidney disease and also to this method of renal replacement therapy [66]. Therefore, we present two cases of chronic hemodialysed male patients to whom PAD was confirmed. The particularity of our report is that both of them, although < 70 years, did not associated diabetes mellitus or smoking history, usually coexistent conditions in this age group individuals with confirmed PAD diagnosis.

CASE DESCRIPTION

The first case is regarding a 64 years chronic hemodialysed oliguric male (diuresis < 300 mL/24h), known with hypertensive nephropathy (as primary renal disease) and dyslipidemia therapeutically controlled (10 mg statin daily). In August 2014, he was admitted for intermittent claudication and ischemic pain at rest. The laboratory tests highlighted elevated nitrogenous waste products (uric acid = 6.18 mg/dL, creatinine = 8.48 mg/dL, BUN = 69.21 mg/dL – equivalent to blood urea of 148.3 mg/dL), cholesterol = 314.25 mg/dL and triglycerides = 180.45 mg/dL, secondary anemia (hemoglobin = 10.50 g/dL), decreased serum iron (57.70 μg/dL), inflammatory status (erythrocytes sedimentation rate = 87 mm/h, fibrinogen = 845 mg/dL), and metabolic acidosis (pH = 7.319, HCO3- = 20.10 mmol/L); the rest of the analysis were in normal range. Additionally, the physical exam emphasized a decreased pulse of the lower limbs and an increased blood pressure (175/100 mmHg). PAD was suspected and therefore an arteriography of the lower limbs was performed in the Interventional Angiography-Cardiology Laboratory of our hospital. The results revealed important atherosclerotic vascular lesions with severe stenosis – 75% stenosis at the origin of left common iliac artery versus 30 – 50% in the opposite limb, and 80% stenosis at the origin of right superficial femoral artery (**Fig. 1 – 5**).

PAD diagnosis was confirmed and revascularization treatment was indicated, but the patient declined. Currently, his therapy consists in peripheral vasodilator, antithrombotic, antiplatelet medication concomitant with statin and hypotensive drugs administration, and allopurinol 100 mg/day, alpha-D3 0,5 μg/day, epoetin beta 5 000 UI (twice per week), iron sucrose supplementation (1 dose per week).

In the second report we described a similar case of a 46 years oliguric male (diuresis < 250 mL/24h), on chronic hemodialysis since 1999, also known with hypertensive nephropathy, dyslipidemia, and no history of smoking or diabetes mellitus. He was admitted in our Department for intermittent claudication and ischemic pain at rest. In addition, his personal medical records revealed an episode of stroke in 2000 with recovered right hemiparesis. The laboratory tests emphasized elevated nitrogenous waste products (creatinine = 7.56 mg/dL, BUN = 64.17 mg/dL – equivalent to blood urea of 137.5 mg/dL), cholesterol = 324.64 mg/dL and triglycerides = 215.15 mg/dL, secondary anemia (hemoglobin = 11 g/dL), decreased serum iron (47.65 μg/dL), inflammatory status (erythrocytes sedimentation rate = 79 mm/h, fibrinogen = 715 mg/dL), and metabolic acidosis (pH = 7.32, HCO3- = 20.90 mmol/L); the rest of the analysis were in normal range. On admission, the physical exam emphasized the absence of the pulse at femoral arteries and an increased blood pressure (180/100 mmHg). PAD was suspected, but arteriography of the lower limbs could not be performed because the patient presented a viable right radiocephalic arteriovenous fistula, a thrombosed vascular access at the left upper limb and no pulse in the femoral arteries. Therefore, thoracic, abdominal and pelvic angio-CT was recommended (performed in the Imagistic Laboratory of our hospital), revealing: aortic athero-sclerotic lesions extended up to the descendent part and aortic arch, atherosclerotic lesions, partially obstructive, in the pelvic arteries, calcified thrombus that partially obstructs the aortic fork (80 – 90% of the caliber), extended up to right common iliac artery, and atherosclerotic injuries in both femoral arteries – 70% stenosis of

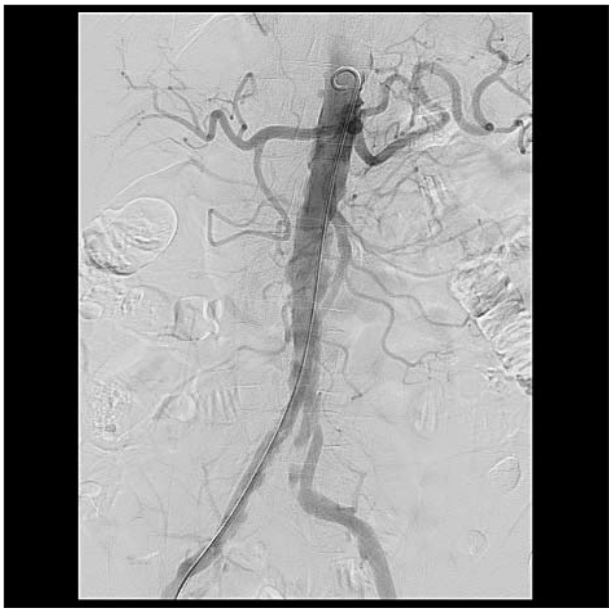

Figure 1. Infrarenal abdominal aorta – diffuse atherosclerotic lesions and permeable renal arteries

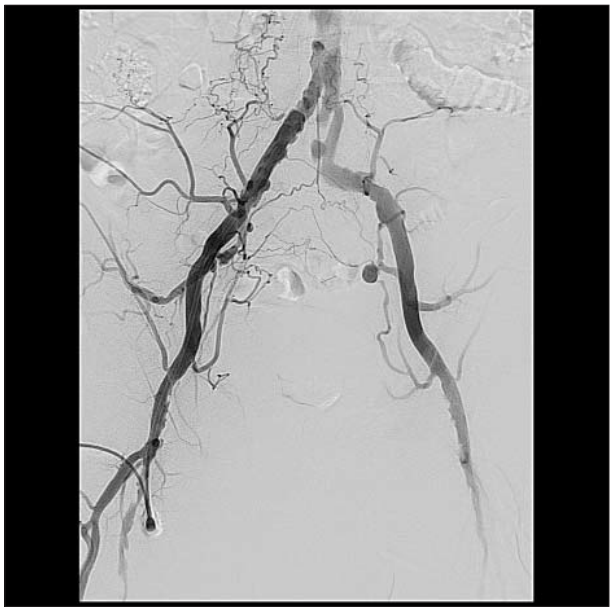

Figure 2. Iliac arterial axis – right axis with diffuse atherosclerotic lesions; left axis with diffuse atherosclerotic lesions and 75% stenosis at the origin of common iliac artery

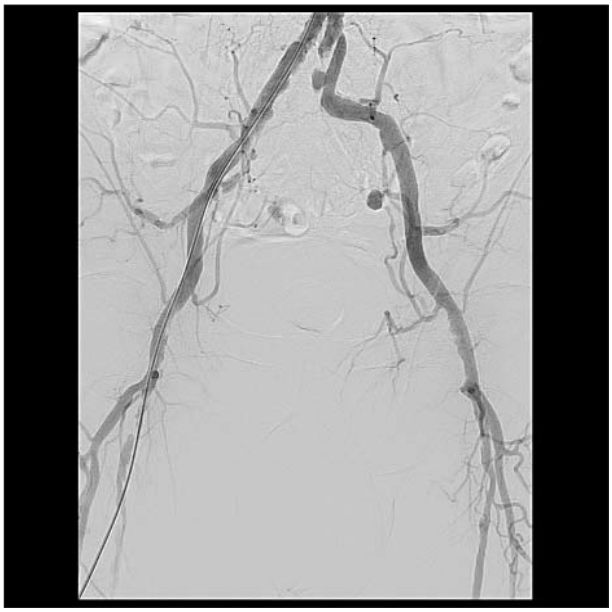

Figure 3. Femoral arteries axis – right axis with common, profound and proximal part of the superficial femoral arteries permeable, but with 80% stenosis at the origin of superficial femoral artery; left axis permeable without significant lesions

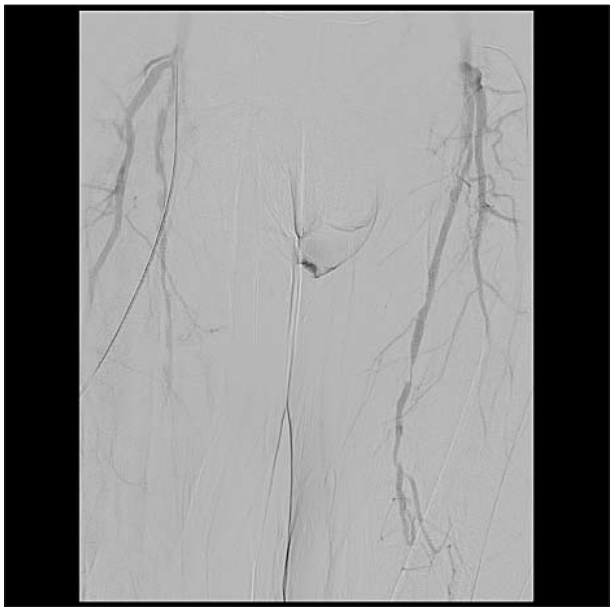

Figure 4. Superficial femoral arteries – right side with occlusive lesions in the median part and poorly developed collateral vascularization; left side with occlusive lesions in the distal part and poorly developed collateral vascularization

the right artery, and 50% of the left femoral artery, respectively (Fig. 6, 7).

Once again, PAD diagnosis was confirmed and several surgical procedures were indicated, but the patient refused, continuing with the palliative therapy (peripheral vasodilator, antithrombotic, antiplatelet drugs) associated with statin, antihypertensives, alpha-D3 0,5 μg/day, epoetin beta 5 000 UI (twice per week), and iron sucrose supplementation (1 dose per week).

DISCUSSIONS

It is already proven that end-stage renal disease, especially after hemodialysis initiation, is associated with

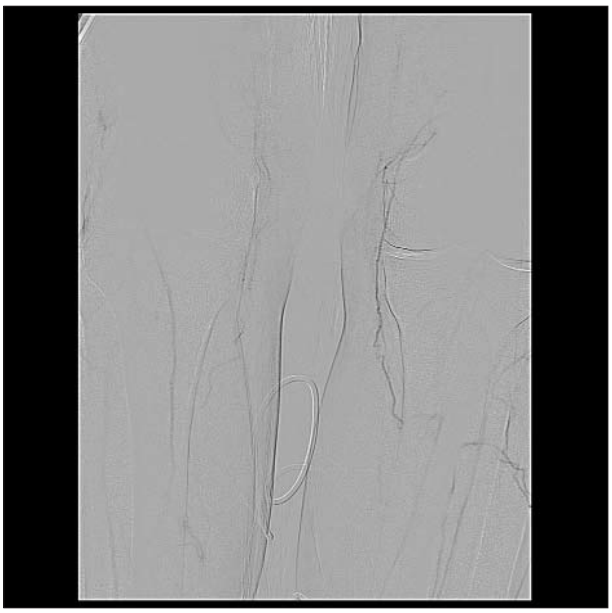

Figure 5. Popliteal artery and leg vasculature – right side with occlusive popliteal artery, decreased perfusion of posterior tibial artery and poorly developed collateral vascularization; left side with occlusive popliteal artery and poorly developed collateral vascularization

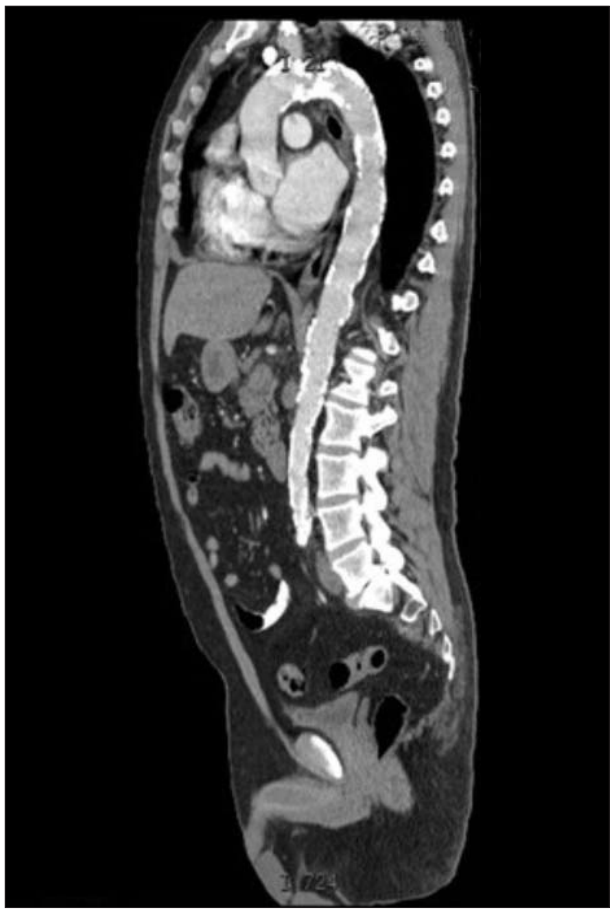

Figure 6. Sagittal plane – significant aortic atheromatosis

increased oxidative stress and inflammatory state [67]. Furthermore, there are consistent data suggesting that not only dialysis per se is an important cause of reactive oxygen species and inflammatory cytokines synthesis, but also the skeletal muscles of these patients are proved to contribute in initiating and elevating the oxidative stress [67], often incriminated in the progression of arteriosclerosis, and consequently in PAD development [68-71].

Another possible explanation for the onset of PAD in hemodialysed patients, even in the absence of diabetes mellitus and long-term smoking history, is provided by the anticoagulant therapy administered in this particular group of population. There are studies concluding that heparin treatment can induce anti-platelet factor 4/heparin antibody synthesis which was correlated with abnormal ankle brachial index values in hemodialysed patients, contributing in this manner to a higher susceptibility of PAD development and progression [72].

Other clinical trials emphasized a clear correlation between low-density lipoprotein apheresis and improvement of oxidative stress and consequently of the PAD symptomatology, but the underlying mechanisms are still not entirely understood [68].

Our findings reporting PAD in long-term hemodialysed patients in the absence of diabetes mellitus and tobacco abuse are in accordance with literature data which describe a possible link between oxidative stress and important inflammatory state induced by several factors (dialysis per se, administered therapy etc) and PAD onset and evolution in this category of individuals.

CONCLUSIONS

Although significant progresses have been achieved for a correct perception of the complexity of the underlying conditions responsible for initiating and progression of peripheral artery disease, further experimental and clinical trials are required to understand the magnitude of this problem in order to include oxidative stress and chronic inflammation as pieces in a bigger puzzle, and to improve the therapy management in order to slow the pathophysiological mechanisms responsible for the evolution of this disease.

Acknowledgement

"This work received financial support through the project entitled "CERO – Career profile: Romanian Researcher", grant number POSDRU/ 159/1.5/S/135760, cofinanced by the European Social Fund for Sectoral Operational Programme Human Resources Development 2007-2013."

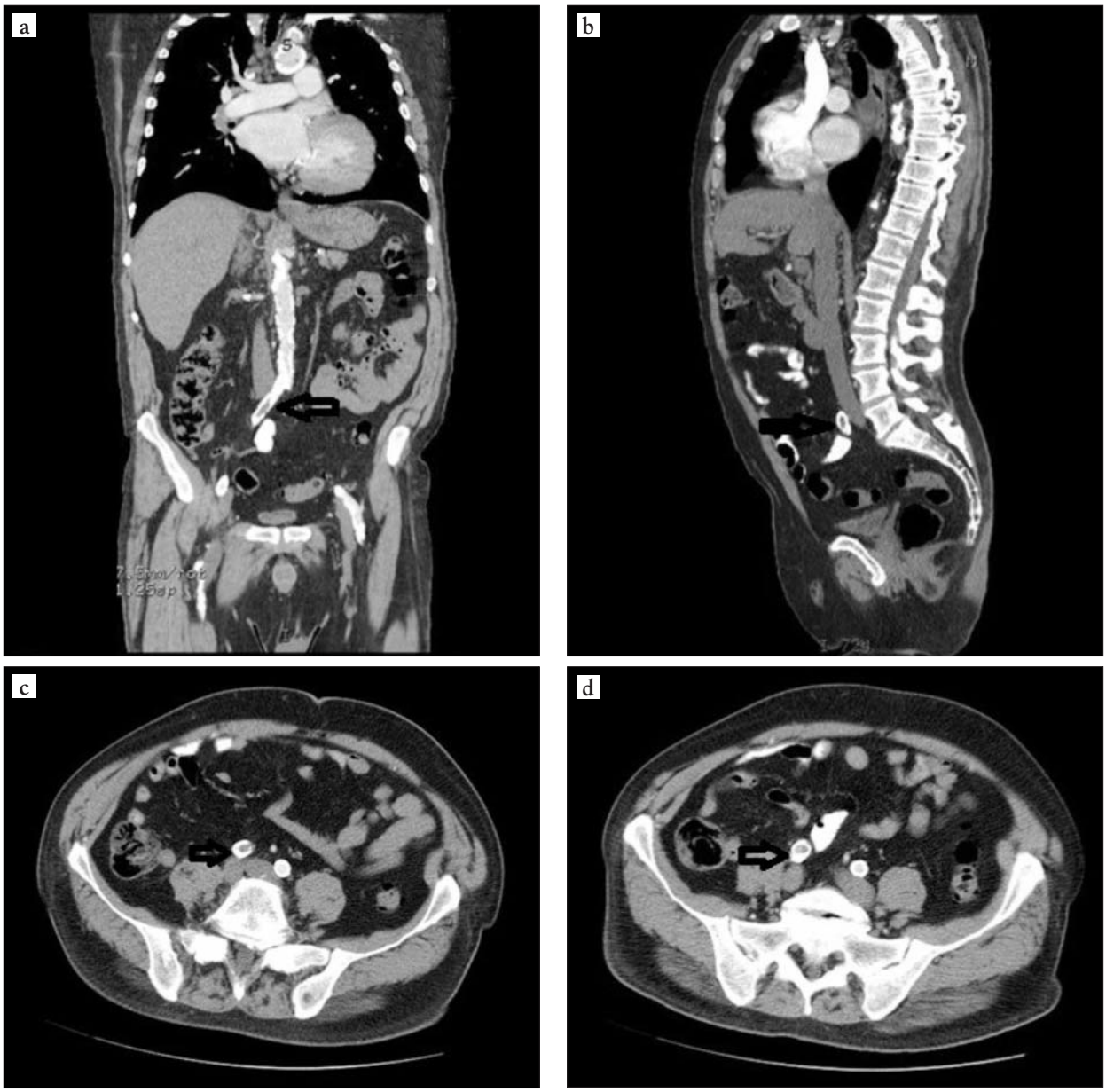

Figure 7. Calcified thrombus that partially obstructs the aortic fork, extended up to right common iliac artery (a. coronary plane; b. sagittal plane; c and d. axial plane)

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