Peripheral vascular disease: prevalence, mortality and association with inflammation in haemodialysis

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SUMMARY

Peripheral vascular disease (PVD) is a common disease among patients undergoing hemodialysis leading to increase morbidity and mortality with a high risk of inflammation and sepsis. The aim of the present study was to determinate PVD prevalence in our hemodialysis population and association with inflammation. The study sample consisted of 220 patients prevalents in hemodialysis. A basal study was made in 2001 and a follow up for 47 months. Data were collected retrospectively. PVD diagnosis was made attending to limb pulses and doppler in revisions. Diagnosis was classified as rest pain, ischemic ulceration and gangrene. Among a total of 220 patients, 89 had prevalent PVD. Thirty per cent had rest pain, 6,5% had ischemic ulceration and 3% had gangrene. Ninety five per cent underwent medical treatment, 0,5% were treated by percutaneous transluminal angioplasty (PTA), 2% were treated with surgical revascularization and 2,5% were treated with amputation. Patients with PVD were older, with higher Charlson index, diabetes, they hay higher CRP and fibrinogen serum levels; and lower albumin and prealbumine serum levels. Survival PVD was decreased in Kaplan-Meier (log rank 012,4; p < 0,000). Adjusted Cox regression analysis revealed that PVD (p = 0,034; OR = 2,10; IC [1,06; 4,23]) ; age (p = 0,001; OR = 1,06; IC [1,03; 1,09]) and low serum albumin levels (p = 0,012; OR = 0,93; IC [0,89; 0,98]) predicted significantly the risk of mortality. PVD is an independent mortality risk factor in hemodialysis patients. An early diagnosis and treatment are able with examination and doppler. In our sample, a few patients are treated with PTA or surgical revascularization. There is an association between PVD and inflammation.

Key words: *Peripheral vascular disease. Hemodialysis. Inflammation. Mortality.*

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RESUMEN

La enfermedad vascular periférica es una complicación frecuente en la población en hemodiálisis que contribuye a aumentar su morbi-mortalidad, al favorecer el estado inflamatorio, la malnutrición y las complicaciones severas como la isquemia y la sepsis secundaria. El objetivo del estudio fue analizar la prevalencia de enfermedad vascular periférica en nuestra población en hemodiálisis, su repercusión en la mortalidad y su asociación con parámetros de inflamación y malnutrición. Fueron incluidos 220 pacientes prevalentes en hemodiálisis, del área perteneciente a nuestro centro hospitalario. Se realizó un estudio basal en el año 2001 y se siguieron durante 48 meses. La enfermedad vascular periférica fue diagnosticada en función de los datos recogidos de las historias clínicas. Se clasificó en ausencia, claudicación intermitente, úlceras o necrosis. De los 220 pacientes, el 39,5% padecía EVP. La clínica más frecuente fue claudicación intermitente (30%), seguida de úlceras (6,5%) y necrosis (3%). El 95% recibió tratamiento médico, el 0,5% fue tratado con angioplastia, el 2% con by-pass y se amputó al 2,5%. En el análisis univariante los pacientes con EVP eran más mayores, con mayor índice de Charlson, diabéticos, tenían niveles séricos más elevados de PCR, fibrinógeno y menores de albúmina y prealbúmina; con respecto a los libres de enfermedad. La supervivencia de los pacientes con EVP fue significativamente menor, analizando la curva Kaplan-Meier (log rank = 12,4; p < 0,000). En el análisis de Cox, los factores que se asocian de forma independiente a la mortalidad son la EVP (p = 0,034; OR = 2,10; IC [1,06 ; 4,23]), la edad (p = 0,001; OR=1,06; IC [1,03; 1,09]) y los niveles bajos de prealbúmina (p = 0,012; OR = 0,93; IC [0,89; 0,98]). La enfermedad vascular periférica es una complicación frecuente en la población en HD, que se asocia frecuentemente a un estado inflamatorio y a un mayor riesgo de mortalidad. Su diagnóstico precoz, mediante interrogatorio dirigido o con exploraciones complementarias, es obligado para iniciar tratamiento.

Palabras clave: Enfermedad vascular periférica. Hemodiálisis. Inflamación. Mortalidad.

INTRODUCTION

Peripheral vascular disease (PVD) is a common condition in the population on haemodialysis, with an estimated prevalen-

ce ranging from 17% and 48% in the different series reported.[1,2] The reason for such a wide range is not clear. It is probably due to the great incident and prevalent variability existing in the literature because of the different forms in which diagnosis is made, i.e. the wide variation in diagnostic criteria and the high percentage of cases with silent PVD in its early stages that is not always considered as disease.

PVD causes an increased morbidity and mortality in the general population because of both the triggering factors (age, smoking, high blood pressure, dyslipidemia, or diabetes mellitus) and its potential complications (ischaemia and sepsis),[3] but its estimated mortality in the haemodialysis population is even greater because of the influence of a number of additional factors, including the chronic inflammation and malnutrition status secondary to both kidney disease and renal replacement therapy, and increase in the calcium-phosphorus product and development of secondary vascular calcifications.[1,4] The crude annual mortality rate from stage V chronic kidney disease on haemodialysis in Spain is 14%, and is associated to the presence of cardiovascular events.[5]

In any case, patients in haemodialysis units are older and have several associated diseases and a high rate of diabetes mellitus. The prevalence of PVD may therefore be expected to gradually increase in the coming years. However, while universally accepted guidelines are established for early diagnosis and management of coronary disease associated to haemodialysis, no protocols that could contribute to improve survival and quality of life are available for patients with PVD.

The objective of this study is to report the prevalence of PVD in our setting and to analyse its relationship to comorbidity, the inflammatory status, and mid-term mortality.

MATERIALS AND METHODS

Prevalent HD patients aged 18 years or older ascribed to a health area of Madrid as of June 2001 (a total of 220 patients) were enrolled into the study.

This was a descriptive, retrospective study that analysed whether patients had in June 2001 PVD, of what grade, and the treatment administered, if any. A number of variables that could influence the risk of death were analysed. Patients were followed up for 48 months, i.e. until June 2005, when the status of each patient was analysed.

The clinical records of all patients were reviewed for the following data: sex, age, cause of renal failure, diabetes mellitus, grade of PVD, treatment of PVD, Charlson comorbidity index, C-reactive protein, albumin, prealbumin, fibrinogen, erythropoietin resistance index, interleukin-6, and patient status at study end.

PVD was diagnosed based on patient symptoms or when the disease was detected by supplemental examinations at revisions in asymptomatic patients. In all patients with clinical signs, diagnosis was confirmed using imaging tests such as echo-Doppler of lower limbs or segmental pressures.

The grade of PVD was rated based on clinical criteria: none, intermittent claudication, ischaemia/ulcers, and necrosis.

Treatment for PVD was classified as medical treatment, angioplasty, bypass, and amputation. Medical treatment was based on antiplatelet aggregants and pentoxyfylline.

The Charlson comorbidity index is a widely used index to measure patient morbidity. It is particularly useful and commonly used in the population on haemodialysis. The following personal history data are considered to calculate the Charlson index: acute myocardial infarction, congestive heart failure, chronic pulmonary disease, rheumatological disease, hepatic disease, gastroduodenal ulcer, renal disease, diabetes mellitus, cerebrovascular disease, dementia, hemiplegia, peripheral vascular disease, neoplasm, or VIH disease.[6]

The erythropoietin resistance index is a parameter calculated as the weekly erythropoietin dose received by each patient (in international units per kg of weight) divided by haemoglobin (in g/dL).

The status of each patient as of May 2005 was classified as death, active on haemodialysis, transplanted, or mover to another unit. The date of the event causing patient withdrawal from follow-up was also recorded.

STATISTICAL ANALYSIS

A Kolgomorov test was used to identify normally distributed variables, that were expressed as the mean and standard deviation (SD). A logarithmic transformation was used to achieve normal distribution of some variables, such as CRP. Variables not having a normal distribution were expressed as median and 95% confidence interval. To analyse qualitative variables and compare proportions, a Chi-square test or a Fisher's exact test was used as appropriate. A Student's t test for independent samples was used to compare quantitative variables. Survival curves were calculated using the Kaplan-Meier method and compared using a log-rank test. Independent variables predicting for mortality were studied using a Cox regression. All probability values less than 0.05% were considered significant. SPSS.13 software was used for data processing and analysis.

RESULTS

Characteristics of the study population

Among the 220 patients enrolled into the study, 124 were males (56%) and 96 females (44%), with a mean age (SD) at study start of 62 ± 14 years. Age ranged from 23 and 88 years. Time of patients on haemodialysis ranged from one month and 26 years, with a mean (SD) of 69.9 ± 67,3 months. The most common cause of renal failure was chronic glomerulonephritis in 41 patients (18.6%), followed by an unknown etiology in 37 patients (16.8%) and diabetic nephropathy in 18 cases (8.2%). Forty-seven patients had diabetes mellitus (21.4%). The mean Charlson comorbidity index was 6.0 ± 5.1. The erythropoietin resistance index was 10.7 ± 8.8 IU/kg/week/g/dL, with a mean haemoglobin value of 12.9±1.7. Table 1 describes the characteristics of the laboratory parameters found in he study.

Characteristics of patients with PVD as compared to healthy subjects

Prevalence of PVD was 39.5%, i.e. 89 of the 220 patients studied.

Table I. Description of laboratory parameters

Variables	Mean	Standar deviation
CRP (mg/dL)	1.3	1.2
Albumin (g/dL)	3.8	0.5
Prealbumin (mg/dL)	29.0	8.4
Fibrinogen (mg/dL)	458	132
Haemoglobin (g/dL)	12.9	1.6

Information about the grade of PVD was collected from 212 patients. Of these, 89 patients had PVD.

The most common clinical sign was intermittent claudication, seen in 65 patients (30%). In asymptomatic patients, PVD was diagnosed using imaging tests. Fifteen patients (6.5%) had ischaemia or ulcers in lower limbs, and 9 patients (3%) showed signs of necrosis.

As regards treatment, 95% received medical treatment, while 1 patient was treated with angioplasty (0.5%), 4 were treated with bypasses (2%), and 5 underwent amputations (2.5%). All patients undergoing amputations had diabetes mellitus.

A significant association was seen between patients with PVD and the following variables: age, etiology of renal failure, diabetes mellitus, Charlson comorbidity index, C-reactive protein, albumin, prealbumin, and fibrinogen (table II).

No statistically significant association was found between the presence of PVD and sex, follow-up time of each patient, time on haemodialysis, and erythropoietin resistance index.

Status at study end, mortality, and associated factors

The study population was followed up for 47 months. At the end of the study, 36.8% of patients continued on haemodialysis, 37.3% had died, 22.7% had undergone a transplant, and 3.2% had been transferred to another hospital.

A higher mortality was seen in the group of patients with more severe PVD, as shown in figure 1. Crude mortality in the study population was 6%, 18%, and 24% at 1, 2, and 3 years respectively.

Mortality associated to PVD

Forty-eight of the 87 patients with PVD had died (55.2%). Survival of patients with PVD was significantly shorter, as shown by the Kaplan-Meier curve (Figure 2), with a log-rank of 12.42 ($p = 0.0004$) as compared to subjects with no PVD.

A higher mortality was found among patients with an older age, higher Charlson indices, greater CRP and fibrinogen levels, and low albumin and prealbumin levels. The presence of PVD, advanced age, and low prealbumin levels was independently related to mortality.

With regard to relationship between treatment and status, the patient treated with angioplasty (0.5%) continued on haemodialysis, while among the 4 patients undergoing bypass surgery (1.9%), 2 continued on haemodialysis (50%), one had died (25%), and one had received a transplant (25%). Of the 5 patients undergoing amputations (2.5%), 4 had died (80%) and one continued on haemodialysis (20%).

Table II. Univariate analysis

	PVD	No PVD	p
Age (years)	67.5 ± 10.1	58.5 ± 16.3	0.000
Diabetes mellitus (yes/no)	36/51	11/122	0.000
Charlson index	5.9 ± 5.0	1,9 ± 1,8	0.000
Albumin (g/dL)	3.6 ± 0.5	3.9 ± 0.4	0.000
Prealbumin (mg/dL)	27.5 ± 9.2	30.0 ± 7.7	0.02
Fibrinogen (mg/dL)	486 ± 138	440 ± 126	0.01
CRP (mg/dL)	1.7 ± 1.8	1.0 ± 1.3	0.001
Epo resistence index (IU/wk/kg/g/dL)	11.1 ± 8.6	10.4 ± 9.0	0.58

DISCUSSION

The prevalence of PVD in the population on haemodialysis in our study was 40%, which is in the upper normal range reported in the literature (from 17% to 48% depending on the series).[1,2] While enrolment criteria in both these studies were similar to those used in our study, including personal history, physical examination findings, and diagnostic tests, they reported that the proportion doubled when diagnostic tests were used as the screening method. The high prevalence of chronic glomerulonephritis and the low prevalence of diabetic nephropathy in our population should be noted. In our opinion, this is related to the high mortality in patients with diabetic nephropathy on haemodialysis.

This study has a number of limitations. It was a descriptive, retrospective study, which makes it difficult to determine the incident cases of PVD. A search for prevalent cases could only be made. The time of diagnosis, the time since disease onset, and whether the condition was present in prior stages of chronic kidney disease were difficult to establish. All cases of PVD had been documented with imaging tests. However, due to the design characteristics, there may be a proportion of asymptomatic patients with silent vascular disease who were not performed imaging tests at revisions. Diagnosis of PVD is therefore difficult and requires objective assessments, mainly in early disease stages. Supplemental tests are not routinely performed in all patients because of their high costs and no proven benefits.

An analysis of risk factors in patients developing PVD showed that this was associated to both classical risk factors, similar to those of the general population,[1,3,4,7] and to factors unique to the uremic population. Moreover, chronic kidney disease, together with diabetes mellitus, is a risk marker for PVD occurrence and poor outcomes. Our study showed PVD to be associated to elderly and diabetic patients, but no significant sex association was seen.

Patients on haemodialysis have a number of additional risk factors related to chronic kidney disease and to treatment itself.[1,3] The calcium-phosphorus product increases in early stages of kidney disease, with development of vascular calcifications. Inflammation and malnutrition also occur in early kidney disease stages, and worsen when replacement therapy is started because proteins and water soluble vitamins are lost in each session and blood contact with dialyser membranes also trigger an inflammatory response with increased levels of C-reactive protein and proinflammatory cytokines that sti-

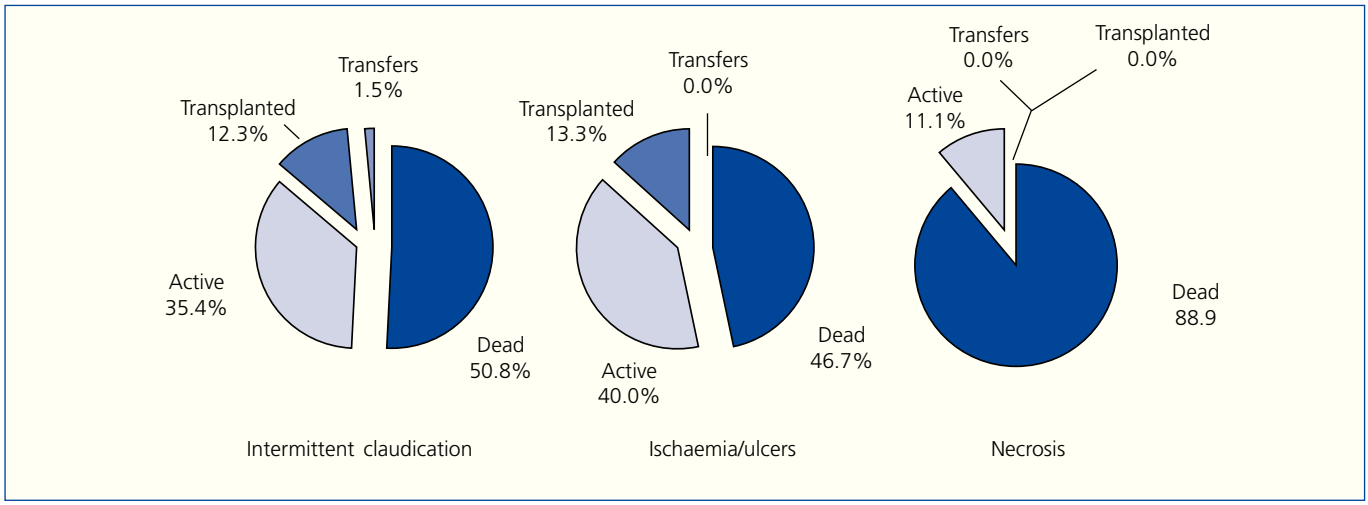

Figure 1. Relationship between status and PVD grade.

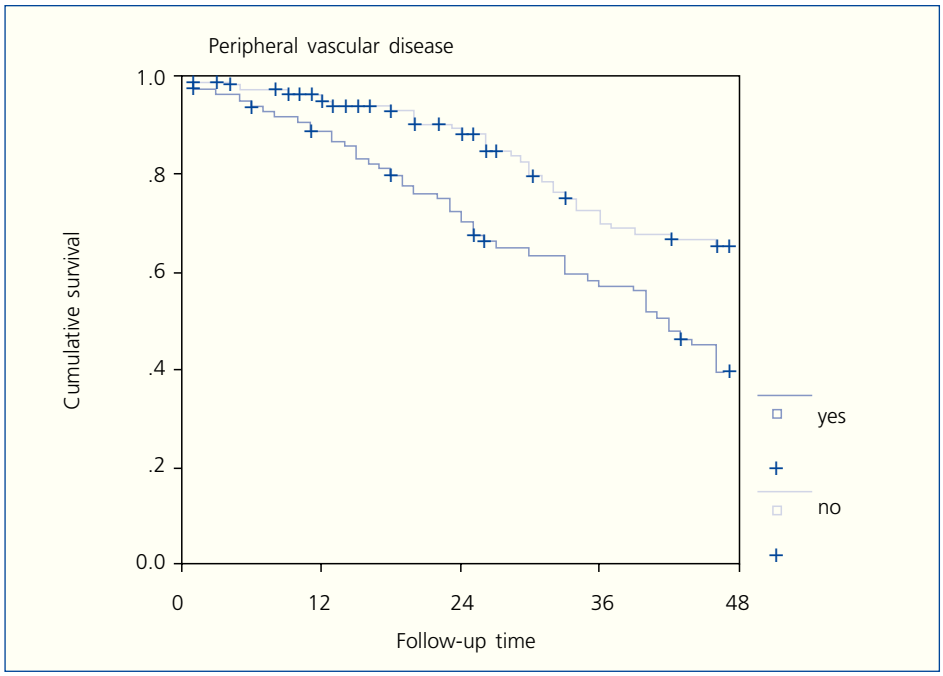

Figure 2. PVD survival according to Kaplan-Meier.

mulate protein catabolism.[8] This results in increases in oxidative stress, endothelial dysfunction, and secondary atherosclerosis.[9,10] Our study tried to focus on epidemiological, comorbidity, and inflammation data, and significant factors such as smoking, calcium-phosphorus product, or characteristics of haemodialysis were therefore not studied. A significant association was found between PVD and inflammation and malnutrition markers such as C-reactive protein, fibrinogen, and decreased albumin and prealbumin levels A very high proportion of patients on dialysis, higher than 30%, have malnutrition,[11] which has an unfavourable influence on survival.[12] Among all poor prognostic markers, plasma albumin levels lower than 4 g/dL were the laboratory finding most closely associated to risk of mortality. Such association was substantial when plasma albumin levels were lower than 3 g/dL.[13] One of the main criticisms made to hypoalbuminemia as a determinant of mortality is that it may not only be a marker of malnutrition, but may also indirectly indicate an increase in circulating volume (haemodilution) or result from a systemic inflammatory response (decrease hepatic synthesis).[14] Together with serum albumin, a non-specific inflammation marker such as serum levels of C-reactive protein has been related to mortality and morbidity in patients with renal failure.[15] Under normal conditions, C-reactive protein (CRP) levels are 0.2 mg/dL, but may be up to 1 mg/dL in some individuals. Values above 1 mg/dL are considered indicative of clinical inflammation. Vascular wall inflammation is essential for onset and progression of atherosclerosis related to vascular rarefaction events, replacement of contractile fibres by fibrotic areas, and calcification of the latter.[16] The source of this systemic inflam-

Table III. Regression analysis for PVD-associated survival

Variables	p	RR/OR	95,0% CI	
			Lower	Upper
Prealbumin	0.012	0.938	0.892	0.986
Age	0.001	1.055	1.023	1.088
PVD	0.034	2.120	1.059	4.246

matory response in uremic patients is uncertain, but has been closely related to malnutrition and atherosclerotic complications (malnutrition- inflammation-atherosclerosis syndrome [MIA]).[17] Results of the F. Caravaca et al study[18] show the association between the malnutrition, inflammation, and atherosclerosis syndrome and uremic patients before dialysis is started. MIA development may therefore not be fully attributed to the potential inflammation triggers inherent to the dialysis procedure (exposure to non-biocompatible materials or bacterial toxins in the dialysis fluid) as suggested by some researchers.[19] Similarly, uremia severity *per se* does not appear to explain this association either, since patient populations studied with the same severity of renal failure may show a very wide range of C-reactive protein levels. Classification of malnutrition of patients on dialysis into two types has recently been proposed.[20] Type 2, associated to other comorbid processes and inflammation, could be the most prevalent and difficult to treat if no satisfactory control of the associated conditions is achieved. One of the most salient findings in the F. Caravaca et al study[18] demonstrates the great impact of vascular disease on early mortality on dialysis in the younger population, suggesting the significance of rigorous control and prevention of vascular disease from the earliest renal failure stages.

As regards survival, our study showed that patients with PVD have a higher mortality rate as compared to disease-free patients, as demonstrated by the Kaplan-Meier curve. Most of our patients were in early disease stages, i.e., with symptoms of intermittent claudication. The risk of death was already significantly greater at this stage.[2,21]

Early diagnosis of PVD may be difficult, as the disease may develop in a silent form.[2] Savage et al[22] found in a study that 75% of 24 patients with stage V chronic kidney disease, but with no clinical signs of PVD, had calcified plaques in the carotid and femoral arteries. In addition, the standard diagnostic methods used once symptoms have already occurred may not be helpful due to small vessel calcifications.[2,23] In any case, screening methods should be implemented at our haemodialysis units to monitor and control the disease, and a segmental pressure study should be performed if distal pulses are absent or routinely in patients with risk factors.

As regards treatment, the low proportion of patients undergoing interventional treatment in our study should be noted: bypass surgery, angioplasty, or amputation were performed in only 5% of patients probably because of late disease diagnosis or a high morbidity making an invasive approach difficult. There are no studies available about whether bypass or angioplasty should be performed. Angioplasty is generally used in cases of intermittent claudication, but bypass is being increasingly used at this stage of disease.[2,24-26] A study[27] showed a greater increase in overall mortality among patients on haemodialysis treated with bypass as compared to those treated with angioplasty.

Incidence of amputation in the United States is ten times higher in patients on haemodialysis as compared to the general population.[2,28] Diabetes mellitus is known to be the main risk factor for amputation in the haemodialysis population.[29] Male sex, a prior diagnosis of PVD, systolic hypertension, and hyperphosphoremia are also predictors of amputation in the newt two years.[30] Special attention must therefore be paid to patients with these characteristics, and an attempt must be made to control or treat modifiable risk factors. Since the mortality rate after amputation is extremely high in the population on haemodialysis,[10,28,31-34] strategies should be implemented to prevent amputation, i.e. to slow disease development.[31,35,36]

In summary, PVD is a common complication in the HD population that is often associated to an inflammatory state and an increased mortality risk. Early diagnosis of PVD by oriented questioning or supplemental examinations is therefore mandatory to start treatment.

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