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Factors associated with lower-extremity amputations in haemodialysis patients

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ABSTRACT

The increasing incidence of lower-extremity amputations in dialysis patients is associated with substantial morbidity and mortality and may be caused by multiple risk factors. The aim of this study was to assess retrospectively the factors associated or predisposing to amputation, through the analysis of epidemiological, clinical and laboratory variables and vascular calcifications (VC) in our chronic haemodialysis (HD) patients over a 2-year period. VC were evaluated using a simple vascular calcification score based on plain X-ray of hands and pelvis.

We studied 258 patients (54.2% males) with a mean±SD age of 63.2±16.1 years, on HD for 39.6±35.8 months. Twenty four patients were amputated (A) and 234 were non-amputated (NA). Demographic characteristics were similar in both groups.

Comparing the two groups, A *vs.* NA, the statistically significant risk factors were diabetes mellitus (DM) 75% *vs.* 21.8 % (p<0.001) and coronary artery disease (CAD) 58.3% *vs.* 25.6% (p=0.001). Group A patients had more hospitalisation days; 25.5 (2-413) *vs.* 12.0 (1-164) (p<0.001) and higher mortality; 37.5% *vs.* 18.4% (p=0.026). Group A also had higher values of C-reactive protein (CRP); 1.4 mg/dL (0.5-21.1) *vs.* 0.8 (0.5-9.4) (p=0.008), glycosylated haemoglobin; (HbA_{1C}) (%) 8.1±1.3 *vs.* 7.1±1.5 (p=0.038) and lower values of urea reduction rate (URR) (%) 72.0±4.8 *vs.* 74.9±7.8 (p=0.014). Group A patients also had a higher VC score (p<0.001).

Using multivariate analysis, the predictors of amputation were DM (p<0.001), CAD (p=0.001), CRP≥3 mg/dl (p=0.004), HbA_{1C}≥6.5% (p=0.02) and VC (p=0.01). We conclude that, in our population, DM (especially if poorly controlled), CAD, an existing inflammatory state (CRP≥3 mg/dl) and the presence of VC were risk factors for lower-extremity amputations. The amputated patients also had more hospitalisation days and a greater mortality than the non-amputated.

Key-Words:
Haemodialysis; lower-extremity amputation; peripheral vascular disease.

INTRODUCTION

Lower-extremity amputation is more frequent in end stage renal disease (ESRD) patients than in the general population[1,2], causing substantial morbidity and mortality. Despite efforts to improve the quality of ESRD care during the last decade, the incidence of lower extremity amputations in dialysed patients has been increasing[1,2].

Multiple risk factors, particularly age, male gender, diabetes mellitus, smoking, hypercholesterolemia, a previous history of peripheral vascular disease and/or cardiovascular events, hyperphosphataemia,

elevated Ca x P product and longer time on dialysis therapy, have been associated with an increased risk of future amputation in chronic HD patients[2-4]. In spite of that, there are very few studies in this area and the existing ones have a short follow-up time. Also, to our knowledge, there are no studies that have analysed risk factors for amputation in dialysed patients in Portugal. Therefore, the aim of this study was to assess the factors associated or predisposing to amputation in our chronic HD patients.

PATIENTS AND METHODS

Study design

This was an observational and retrospective study, which analysed prevalent chronic HD patients treated in a single-centre in a 2 year period (January 2001 – January 2003).

Population

The study included 258 patients, 234 non-amputated (NA) and 24 amputated (A). All patients were dialysed with high flux membranes (helixone-Fresenius®) and ultrapure water.

The mean age was 63.2±16.1 years and 54.2% of the patients were males. Mean HD time was 39.6±35.8 months.

Methods

A prior and current history of diabetes mellitus and/or hypertension was investigated in all patients. Coronary artery disease was diagnosed if the patient had a typical history of angina pectoris or had suffered a myocardial infarction, had a positive stress test or had undergone a percutaneous coronary procedure or coronary bypass surgery. Diagnosis of cerebral vascular disease was based on the occurrence of stroke or transient ischaemic attack or the detection of an old cerebral infarction using computed tomography.

In the 2-year period of the study, hospitalisation days and mortality in both groups were evaluated retrospectively.

Serum calcium, serum phosphorus, Ca x P product, total intact parathyroid hormone (iPTH), bone alkaline phosphatase, C-reactive protein (CRP), albumin, fibrinogen, β2-microglobulin, urea reduction rate (URR) and glycosylated haemoglobin (HbA_{1C}) were all measured monthly. Total iPTH was evaluated by immunochemiluminescence using a second generation assay.

To evaluate vascular calcifications we used a simple vascular calcification score developed by Adragão *et al* [5]. This vascular calcification score is based on the analysis of plain X-ray films of pelvis and hands. Pelvis films were divided into four sections by two imaginary lines: a horizontal line over the upper limit of both femoral heads and a median vertical line over the vertebral column. Hand films were divided for each hand by a horizontal line over the upper limit of the metacarpal bones. Pelvis films evaluated iliac and femoral arteries (ileo-femoral score) and hand films evaluated radial and digital arteries (hand score). Any vascular calcification lining the vessel walls in either an irregular or linear pattern was considered. The presence of vascular calcifications in each section was rated as 1 and its absence as 0. Final score was the sum of all sections and ranged from 0 to 8.

Statistical analysis

For statistical analysis the arithmetic media of five measurements – January 2001, June 2001, January 2002, June 2002, January 2003 – was used.

We used the $\chi 2$, Student or Mann-Whitney tests for univariate analysis and logistic regression on multivariate analysis (confidence interval of 95%) for the statistical analysis $p<0.05$ was considered statistically significant.

Statistical analysis was performed with SPSS system 11.0 (SPSS Inc., Chicago, IL).

Results

Of the 258 chronic HD patients evaluated, 26.7% (n=69) had diabetes mellitus, 69.8% (n=180) hypertension, 28.7% (n=74) coronary artery disease and 17.8% (n=46) cerebral vascular disease. The prevalence

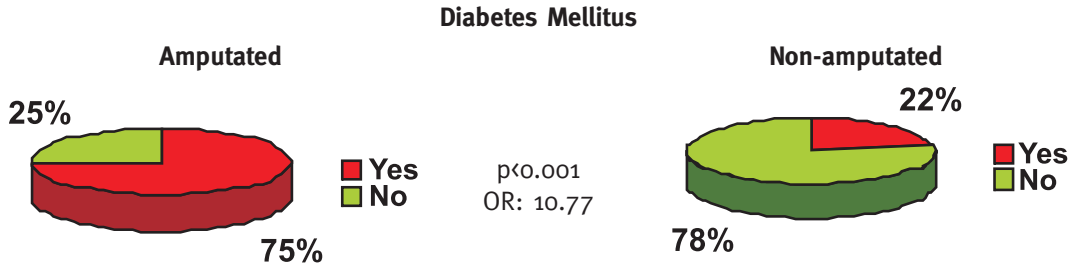

Figure 1

The prevalence of diabetes was significantly higher in group A.

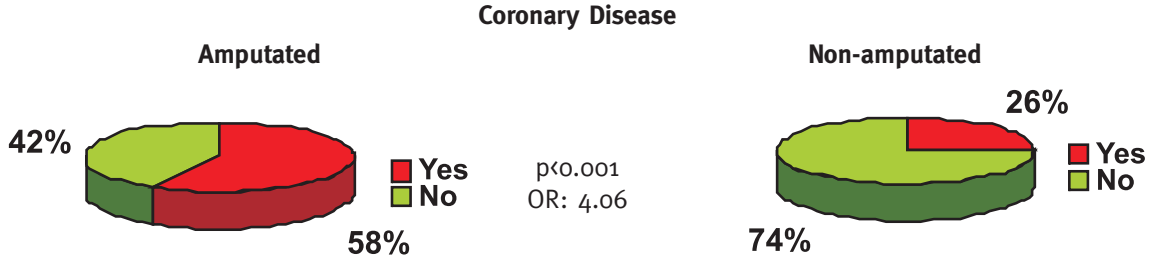

Figure 2

Group A showed a significantly higher frequency of coronary artery disease.

of amputation in the population studied was 9.3% (n=24). Demographic characteristics, such as age, HD duration and gender were similar in both groups (A and NA).

Comparing the two groups A and NA, 75% (n=18) of the patients in group A were diabetics *vs.* only 21.8% (n=51) in group NA and this difference was statistically significant (OR=10.77, CI~4.06-28.52, p<0.001) (Figure 1). This is unlike hypertension, where the intragroup difference was not significant (p>0.05); A 45.8% (n=11) and NA 72.2% (n=169).

The presence of coronary artery disease was higher and statistically significant in group A; 58.3% (n=14) *vs.* NA 25.6% (n=60) (OR=4.06, CI~1.71-9.62, p=0.001) (Figure 2). The prevalence of cerebral vascular disease was similar in the two groups: (p>0.05); A 20.8% (n=5) and NA 17.5% (n=41).

Morbidity, expressed by the number of hospitalisation days, was higher in group A; 25.5 (2-413) *vs.* NA 12.0 (1-164) (p<0.001), as was mortality; A 37.5 % (n=9) *vs.* NA 18.4% (n=43) (OR=2.67, CI~1.09-6.49, p=0.026).

Concerning laboratory parameters, values of CRP (mg/dl) 1.4 (0.5-21.1) *vs.* 0.8 (0.5-9.4) (p=0.008) (Figure 3) and of HbA_{1C} (%) 8.1±1.3 *vs.* 7.1±1.5 (p=0.038) were higher and values of URR (%) 72.0±4.8 *vs.* 74.9±7.8 (p=0.014) were lower in the A group.

The remaining laboratory parameters, serum calcium, serum phosphorus, Ca x P product, iPTH, bone

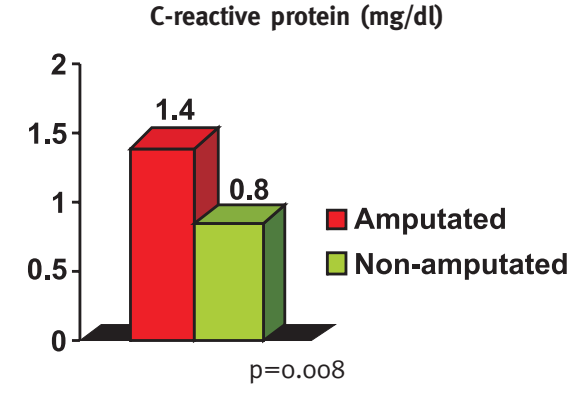

Figure 3.

CRP was significantly more elevated in group A.

alkaline phosphatase, β2 – microglobulin, albumin and fibrinogen, were similar in both groups (p › 0.05) (Table I).

Table I.

Comparison of laboratory parameters in the two groups

Laboratory parameters	Amputated (n = 24)	Non-amputated (n = 234)	*P* value
Calcium (mg/dl)	9.10 ± 0.58	9.21 ± 0.71	NS
Phosphorus (mg/dl)	3.69 ± 0.99	4.34 ± 1.71	NS
Calcium x Phosphate (mg^2/dl^2)	33.80 ± 9.89	40.17 ± 16.55	NS
iPTH (pg/ml)	100.15 (17.6-394.8)	164.56 (6.2-1374.7)	NS
bAP (μg/l)	16.86 (8.4-59.4)	17.83 (3.2-178.8)	NS
C-reactive protein (mg/dl)	1.40 (0.50-21.10)	0.85 (0.50-9.40)	0.008
Albumin (g/dl)	3.69 ± 0.53	3.88 ± 0.38	NS
Fibrinogen	449.82 ± 141.89	449.82 ± 141.89	NS
β2-microglobulin	17162.33 ± 7175.41	20355.25 ± 8081.22	NS
URR (%)	72.08 ± 4.81	74.94± 7.82	0.014
HbA_{1C} (%)	8.13 ± 1.36	7.12 ± 1.52	0.038

Vascular calcifications were evaluated in nearly 70% of the patients (n=178). Patients from group A had a higher calcification score 6.8±1.3 *vs.* 2.4±2.5 (p‹0.001) (Figure 4). Sixty patients (37%) in the NA group had no vascular calcifications, while in group A all patients had vascular calcifications.

Comparing diabetic patients that underwent an amputation to diabetics who had no amputation, the only significant differences were a higher vascular calcification score 6.8±1.4 *vs.* 4.3±2.8 (p=0.018) and more hospitalisation days 23.0 (0-413) *vs.* 9.5 (0-83) (p=0.002) in the group of diabetics who underwent amputation.

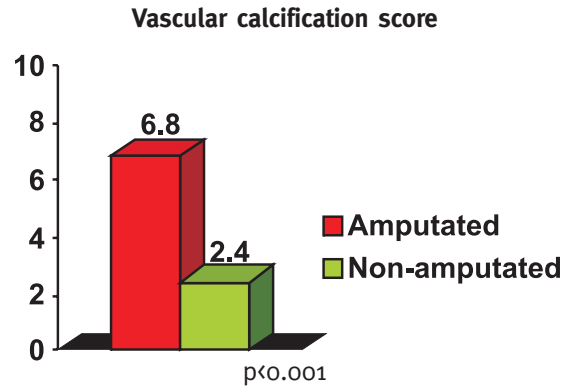

Figure 4

Vascular calcification score was significantly higher in group A.

Using multivariate analysis, diabetes mellitus (OR=10.76, CI~4.06-28.52, p‹0.001), coronary artery disease (OR=4.06, CI~1.71-9.62, p=0.001), CRP≥3 mg/dl (OR=4.06, CI~1.48-11.11, p=0.004), HbA_{1C}≥6.5% (OR=9.16, CI~1.05-79.38, p=0.02) and a higher vascular calcification score (OR=2.07, CI~1.41-3.01, p=0.01) were all positive predictors of amputation.

DISCUSSION

Diabetes mellitus is the main risk factor for lower limb amputation in the general population. In diabetic patients, the presence of vascular peripheral disease, male gender, older age and presence of a more severe disease (poor glucose control, longer duration of diabetes and the presence of retinopathy, nephropathy and neuropathy) are the strongest risk factors for amputation[6].

Although it constitutes an increasing problem with elevated economic and social costs, amputation among patients with ESRD has not been extensively analysed. The main study in this area was carried out by Eggers *et al*[1] and it evaluated the presence of amputation among all Medicare ESRD beneficiaries. In this population, patients whose cause of ESRD was diabetes, hypertension or unknown, were at a greater risk of amputation than those in whom glomerulonephritis was the primary cause. Older age, male gender and black race were also risk factors for amputation. Patients who had undergone renal transplantation had a lower risk of amputation. However, these authors only examined the association of amputation with demographic characteristics, cause of ESRD and transplantation status and did not study other characteristics of this population, namely laboratory values and other comorbid conditions. Furthermore, this study analysed patients with ESRD as a group and did not evaluate the specific subgroup of HD patients.

Some years later, another study performed by O'Hare *et al*[2] in chronic HD patients pointed out other risk factors for amputation, such as male gender, presence of diabetes and previous peripheral vascular disease, elevated mean systolic blood pressure and hyperphosphataemia. In the subgroup of non-diabetic patients, previous cardiac disease and time on HD were the main risk factors for amputation. On

the contrary, other studies showed that amputation is usually an early event occurring within the first 6 months of beginning HD[7,8].

Our analysis verified that diabetes mellitus significantly increases the risk of amputation in a proportion similar to the one found in the general population[9]. Although peripheral vascular disease was more prevalent in diabetics, the amputation itself is mainly associated with the presence of microangiopathy[9]. Thus, an increasing prevalence of microangiopathy in these patients may be determinant to the occurrence of amputation, as well as other cardiovascular events. In our population 58.3% had documented coronary artery disease at the time of amputation, but the prevalence of cerebral vascular disease was not significantly superior in this group.

The association between peripheral vascular disease and coronary artery disease is well established not only in the general population, in which 40% of the patients with intermittent claudication have coronary artery disease[10], but also in patients with chronic renal failure in a similar proportion[11,12].

Age, gender, time on HD and the presence of hypertension were not risk factors for amputation in our population, unlike the majority of the studies in this area.

While considering prevalent patients on HD within a 2-year follow-up period, our study allows the observation of a strong association between morbidity and mortality and amputation, as occurs in the general population.

Laboratory values analysis showed that higher levels of CRP, probably expressing an existing inflammatory state in HD patients, were significantly associated with the presence of amputation. Chronic HD patients with higher inflammatory parameters have an increased risk of vascular calcifications, mainly in the media of the arteries[13,14]. Furthermore, patients with atherosclerosis, a process that mainly affects the intimae of the arteries, also have higher values of CRP[15]. These two processes working together certainly give rise to a higher amputation risk in HD patients.

As described in other studies, lower values of URR were associated with a higher risk of amputation. This relationship between HD inadequacy and amputation risk may be explained by the pathological effects of uraemia, such as a certain infection predisposition[16], presence of polyneuropathy[17], autonomic dysfunction[18] and peripheral vascular disease[19], all of which can be involved in the pathogenesis of lower-extremity amputation. HD inadequacy has been found to be associated with a higher mortality due to coronary artery disease, other cardiac disease, cerebrovascular disease, infection and with all cause mortality[20].

Values of $HbA_{1C} \geq 6.5\%$ were a risk factor for amputation in our study. Studies performed in a non-ESRD diabetic population had already demonstrated an association between poor glucose control and amputation risk, as well as the development of other complications of diabetes[6]. Unlike other studies[2,3], hyperphosphataemia and an elevated Ca x P product were not associated with the presence of amputation, which can be explained by lower levels of both serum phosphorus and Ca x P product obtained in our studied patients, compared to others.

Vascular calcification, namely medial calcification or Monckeberg's arteriosclerosis, is one of the pathogenic factors that has been associated with peripheral artery disease[21]. This is particulary relevant in dialysis patients where mineral metabolism disturbance seems to contribute to vascular disease[13,14]. In this study amputated patients presented a higher vascular calcification score, although there was no difference in serum calcium, serum phosphorus, Ca x P and iPTH between group A and NA, which probably reflects that other factors besides these are involved in the development of vascular calcifications[14].

All amputated patients were followed in Vascular Surgery, but none was considered a candidate for surgical revascularisation, probably due to predominantly distal disease. Although surgical revascularisation is not the definitive solution in most cases, it shoud be pointed out that an early screening for peripheral vascular disease and timely infrainguinal vein bypass in selcted cases can modify the prognosis and avoid primary amputations[21,22]. Foot ulcers (active and old scars) should be taken as indicators of a bad haemodynamic prognosis for revascularisation[22].

In conclusion, our results show an elevated incidence of lower-extremity amputation in chronic HD

patients. The presence of a poorly controlled diabetes mellitus, (with values of HbA_{1C}≥6.5%), coronary artery disease, the existence of an inflammatory state (CRP≥3 mg/dl) and vascular calcifications were all predictors of amputation. As expected, the amputated patients had more hospitalisation days and a higher mortality than the non-amputated.

Conflict of interest statement. None declared.

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