

Gender differences within the clinical risk profile of lower-limb amputee patients

Diferencias según el género en el perfil clínico de riesgo del paciente amputado de miembro inferior

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Abstract

Objectives: To analyze the possible gender differences within the clinical risk profile of lower-limb amputee patients who had a non-traumatic amputation. **Method:** A retrospective study with 697 lower-limb amputee patients, classified according to their gender, has been conducted at the Angiology and Vascular Surgery Department for 5 years. The variables considered were demographic variables (age and gender) and clinic variables (cause of the amputation, comorbidity, cardiovascular risk factors and the amputation level). **Results:** Regarding the results, the average of women was older than men (75.3 ± 12 vs. 68.9 ± 11 years; $p < 0.001$), showing an increasing frequency to concomitant cardiovascular risk factors, such as diabetes, hypertension, and obesity. However, men present a higher frequency to smoking. There were no gender differences in the main cause of the amputation, the ischemic cause, being notably into this cause the subgroup of arteriosclerosis cause. Women showed a higher frequency and predisposition for major amputation. **Conclusions:** This study showed that women had a more unfavorable cardiovascular risk profile than men, being the female gender an independent predictor to a major lower-limb amputation with non-traumatic amputation.

Keywords: Amputation. Lower limb. Gender. Cardiovascular risk factors.

Resumen

Objetivo: Analizar las diferencias según el sexo en el perfil clínico de riesgo de los pacientes amputados de miembro inferior por causa no traumática. **Método:** Estudio retrospectivo descriptivo con 697 pacientes amputados de miembro inferior por causa no traumática, en un Servicio de Angiología y Cirugía Vascular, durante un periodo de 5 años y divididos en función del sexo. Se analizaron variables demográficas (edad) y clínicas (causa, comorbilidad, factores de riesgo cardiovascular y nivel de amputación). **Resultados:** La edad media ($\pm$ desviación estándar) de las mujeres fue mayor (75.3 ± 12 frente a 68.9 ± 11 años; $p < 0.001$) y ellas presentaron mayor frecuencia de factores de riesgo cardiovascular concomitantes, tales como diabetes, hipertensión y obesidad, que los varones, mientras que ellos presentaron mayor frecuencia de tabaquismo. No hubo diferencia significativa entre sexos respecto a la distribución de las causas de amputación, siendo la principal causa

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la isquémica, destacando la arteriosclerosis. Las mujeres presentaron mayor frecuencia y predisposición para un nivel de amputación mayor. **Conclusiones:** En nuestro estudio, las mujeres presentaron un perfil de riesgo cardiovascular más desfavorable y el sexo femenino fue un predictor independiente de amputación mayor de miembro inferior por causa no traumática.

Palabras clave: Amputación. Extremidad inferior. Sexo. Factores de riesgo cardiovascular.

Introduction

In current international panorama, Spain ranks second with regard to the rate of lower limb (LL) amputation for diabetic foot, with evident differences according to gender (4.71 in men vs. 1.75 in women) and only surpassed by the United States of America, with an amputation rate of 3.19 per 1000 population^{1,2}. This is a growing health problem, since while the rate of LL amputations of traumatic or neoplastic origin considerably decreases over time, the progressive increase in the rate of LL amputation due to non-traumatic causes is a fact, despite great advances in the field of surgical sciences.

Analyzing the demographic data of some studies on this type of surgery of last decades³⁻⁵, age must be regarded as a determining factor, since patients are mainly advanced-age individuals, with higher incidence of peripheral vascular disease, cardiovascular risk factors (CVRF) and concomitant pathology. Life expectancy increase in Spain, together with vascular disorders of older age, undoubtedly favor an increase in the occurrence of these events, with age being an essential factor in non-traumatic LL amputation.

In these latest investigations, it also appears that patient gender can be a differential factor, since there is evidence of a clear disparity in LL amputations between genders. Currently, those who are most affected by this type of events are men, at a ratio of approximately 3 to 1^{6,7}. Although gender has not been shown to be a risk factor for suffering a surgical act of this type, it is possible for a specific clinical profile to exist according to one gender in particular, which would explain a higher tendency towards LL amputation in males.

Most part of scientific evidence on which current medical performance in LL amputee patients is based, has been obtained from studies with a higher participation of men. However, we should not ignore that, although men are more affected by these surgical acts, both vascular diseases in general and LL amputations due to vascular causes in particular constitute an important and growing source of morbidity and mortality in women.

Until a few years ago, both scientific institutions-promoted registries and interventional clinical trials have included a minimum proportion of women, thus generating a large scientific gap in the knowledge of this type of events in the female gender.

In this sense, and given the lack of publications about this growing vascular problem addressing both genders with the same in-depth approach, despite the evident disparities between men and women revealed by existing research data, as well as by clinical evidence itself, the main purpose this study is to examine possible gender differences in the clinical profile of patients undergoing LL bifocal amputation due to non-traumatic causes, and thus further contribute knowledge on this complex health dilemma.

Method

Study design

A retrospective, descriptive clinical study was carried out with 697 LL amputee patients at the Angiology and Vascular Surgery Department of San Cecilio University Hospital in Granada, Spain, over a 5-year period, between January 1, 2009 and January 1, 2014.

Sample

The patients were divided in two groups according to gender, and the inclusion criteria were to be of legal age, undergoing LL amputation at the hospital during the study period, and amputation of non-traumatic cause.

Patients amputated on more than one occasion in the study period were recorded by the highest amputation level, to avoid duplications.

Study variables

Two types of variables were analyzed: demographic (age and gender) and clinical variables (CVRF, cause, comorbidity and amputation level).

Evaluated CVRFs included diabetes, hypertension, dyslipidemia, smoking and obesity, which were collected

from patient medical records, using previous diagnosis of these factors documented in the medical record as a criterion. Smoking was defined as the chronic habit of smoking. Obesity was defined as a body mass index ≥ 30 kg/m².

Patients were classified in two groups according to the cause: ischemic and non-ischemic. Within ischemic causes, a distinction was made between arteriosclerotic cause (chronic LL ischemia) and thromboembolic cause (acute LL ischemia). Non-ischemic causes include neuropathic and septic diabetic foot.

The comorbidities that were considered included ischemic heart disease, cardiac arrhythmia, heart failure, renal failure, and diabetic retinopathy. Previous diagnosis of these pathologies documented in the medical record was used as a criterion.

Two amputation level categories were defined, according to the Andalusian Society of Angiology and Vascular Surgery classification⁸: minor amputation (with the heel being preserved) and major amputation.

Statistical analysis

The SPSS program, version 25.0, was used. A comparison of all patient demographic and clinical characteristics was carried out according to gender. Categorical variables were compared using the chi-square test, while continuous variables were compared with ANOVA test. The significance threshold was established at $\alpha = 0.05$.

A multivariate logistic regression model was also constructed to determine the factors associated with major amputation. The logistic regression model included age, gender, and clinical variables that could be related to the need to undergo major amputation. The main prognostic factors for major amputation were regarded as independent variables: age, gender, CVRF and comorbidity.

Results

LL amputee patients demographic characteristics and CVRF distribution according to gender are summarized in table 1. A total of 697 patients, with a mean age of 70.5 years (SD: 11.9), with a minimum of 27 years and a maximum of 98 years, and a median of 72 years, were included. The number of male amputees was three times higher than that of females. The female gender had a significantly higher mean age than the male gender, and a higher percentage were in the age subgroup older than 65 years.

Table 1. Demographic characteristics and cardiovascular risk factors according to gender

	Total patients (n = 697)	Males 74.9% (n = 522)	Females 25.1% (n = 175)	p
Mean age	70.5 $\pm$ 11.9	68.9 $\pm$ 11	75.3 $\pm$ 12	0.001
Median	72			
> 65 years	70.4% (n = 491)	69% (n = 339) M: 64.9	31% (n = 152) F: 86.9%	0.020
CVRF				
Diabetes	78.5% (n = 547)	73.1% (n = 400) M: 76.6	26.9% (n = 147) F: 84%	0.040
Hypertension	58.8% (n = 410)	71% (n = 291) M: 55.6%	29% (n = 119) F: 68%	0.003
Dyslipidemia	33.9% (n = 236)	72.9% (n = 172) M: 32.8%	27.1% (n = 64) F: 36.5%	0.140
Smoking	50.8% (n = 354)	96.3% (n = 341) M: 65.3%	3.7% (n = 13) F: 7.4%	0.001
Obesity	27% (n = 188)	63.8% (n = 120) M: 23%	6.2% (n = 68) F: 8.6%	0.001

CVRF: cardiovascular risk factors; F: females; M: males; SD: standard deviation.

In all cases, the *n* parameter has been rounded to whole numbers, as it indicates the number of affected individuals in the sample.

Diabetes, hypertension and obesity were the CVRFs that were documented most frequently and with a statistically significant difference in women, while smoking significantly predominated in men.

As for comorbidity, there were no statistically significant differences between genders, as shown in table 2. The frequency of major amputation was also analyzed, with a higher proportion being observed in the female gender, with a statistically significant difference.

Table 3 summarizes the analysis of amputation causes, among which no difference was found between men and women with regard to both general causes (ischemic and non-ischemic), with arteriosclerosis standing out in both genders within ischemic causes.

Table 4 shows the results of the multivariate logistic regression analysis. The variables that favor the possibility of suffering major amputation are age, the female gender, diabetes, previous cardiac pathology and diabetic retinopathy, given that they were independent predictors of major amputation.

Discussion

The results of this descriptive clinical study conducted on a large sample of patients who underwent LL amputation for non-traumatic causes show the relevance of gender in these surgical acts. The work,

Table 2. Comorbidity and major amputation according to gender

	Total patients (n = 697)	Males 74.9% (n = 522)	Females 25.1% (n = 175)	p
Major amputation	54.7% (n = 381)	71.4% (n = 272) M: 52.1%	28.6% (n = 109) F: 62.3%	0.019
Comorbidity				
Prior ischemic heart disease	12.1% (n = 84)	76.2% (n = 64) M: 12.3%	23.8% (n = 20) F: 11.4%	0.69
Cardiac arrhythmia	11.6% (n = 81)	74.1% (n = 60) M: 11.5%	25.9% (n = 21) F: 12%	0.69
Prior heart failure	6.2% (n = 43)	67.4% (n = 29) M: 5.6%	32.6% (n = 14) F: 8%	0.69
Prior renal failure	14.3% (n = 100)	74% (n = 74) M: 14.2%	26% (n = 26) F: 14.9%	0.82
Prior diabetic retinopathy	18.5% (n = 129)	78.3% (n = 101) M: 19.4%	21.7% (n = 28) F: 16%	0.71

F: females; M: males.

In all cases, the *n* parameter has been rounded to whole numbers, as it indicates the number of affected individuals in the sample.**Table 3. Amputation causes distribution by gender**

	Total patients (n = 697)	Males 74.9% (n = 522)	Females 25.1% (n = 175)	p
Ischemic cause	71.7% (n = 500)	74% (n = 370) M: 70.9%	26% (n = 130) F: 74.3%	0.62
– Arteriosclerotic cause	64.7% (n = 451)	73.8% (n = 333) M: 63.8%	26.2% (n = 118) F: 67.4%	0.83
– Thromboembolic cause	7% (n = 49)	75.5% (n = 37) M: 7.1%	24.5% (n = 12) F: 6.9%	
Non-ischemic cause	28.3% (n = 197)	77.2% (n = 152) M: 29.1%	22.8% (n = 45) F: 25.7%	0.62

F: females; M: males.

In all cases, the *n* parameter has been rounded to whole numbers, as it indicates the number of affected individuals in the sample.

carried out in an angiology and vascular surgery department of a public hospital, is representative of how the female gender determines a more unfavorable clinical profile.

Amputee females had an average age of 6.4 years more and a higher prevalence of diabetes than males, who only surpassed them in the smoking rate. These findings are similar to those presented in the study by Davie-Smith F et al.⁹ on the impact of gender on the prosthetic adjustment rate after a major LL amputation, carried out in Scotland.

According to recent national¹⁰⁻¹² and international¹³⁻¹⁵ studies, the results of this work show that the most affected by these interventions are men, whose percentage of amputees triples that of women, despite the fact that they have a higher mean age and poorer previous clinical profile.

Table 4. Stepwise logistic regression model predictive of major lower limb amputation in the study population

Major amputation	p	OR (95% CI)
Age	0.008	0.953 (0.947-0.967)
Gender	0.019	1.195 (1.037-1.377)
CVRF		
Diabetes mellitus	< 0.001	1.889 (1.691-2.109)
Hypertension	0.170	1.236 (0.913-1.674)
Dyslipidemia	0.873	1.026 (0.749-1.406)
Smoking	0.704	1.059 (0.786-1.428)
Obesity	0.187	0.978 (0.699-1.368) 0.821 (0.697-1.077)
Comorbidity		
Prior cardiac pathology	0.002	1.674 (1.200-2.336)
Prior renal impairment	0.886	0.969 (0.634-1.486)
Diabetic retinopathy	< 0.001	1.503 (1.197-1.888)

CI: confidence interval; OR: odds ratio.

However, although the frequency of amputation is much lower in women, the proportion of major amputations observed in them significantly exceeded that of men.

From the pathophysiological point of view, the CVRFs present in the patient play an essential role in the outcome of this type of surgical events, since they largely determine amputation level, evolution and prognosis.

The fact that more than three quarters of amputations in patients of the sample of this study were driven by an ischemic-type vascular problem of the LL reinforces the importance of patient previous cardiovascular profile, which would be in line with findings of other publications¹⁶⁻¹⁸, which also highlight the importance of CVRFs on LL amputation.

In addition to a poorer clinical profile in amputee females, it is possible for them to have gender-specific characteristics that favor a higher level of amputation than in men, despite the low frequency of these interventions in comparison with males.

These gender-associated differential aspects, evident in routine clinical practice, and that could favor both a poorer cardiovascular profile and a higher level of amputation in females, are not yet well characterized, mainly due to insufficient inclusion of women in clinical trials and in other studies on this type of surgery.

Analyzing the different CVRFs, in the case of diabetes there are studies that show an increase in blood-glucose levels and in the incidence of type 2 diabetes with age in both genders, although with a

clear predominance of the female gender¹⁹⁻²¹. These publications show a predominance of the female gender in response to a higher presence of obesity with increased insulin resistance, disproportionate body fat distribution, loss of estrogen protective function and longer life expectancy in women. The results of this study show significant differences in the distribution of this CVRF among amputee patients according to gender, with a higher prevalence of diabetes in women, as referred by said publications. According to Peters et al.²², further deterioration of the cardiovascular risk profile, combined with longer exposure to CVRF in prediabetic women, possibly due to higher adiposity, may be the cause of the excessive risk of coronary heart disease-related diabetes in women. These same authors, in another study of similar nature to the previous one²³, show that excess stroke risk is higher in women, regardless of gender differences in other CVRFs, and suggest that it should be taken into account that men and women experience diabetes-related diseases differently. With no doubt, the findings of this study are consistent with those of these authors, since the female gender had a higher incidence of diabetes, associated with a higher presence of other relevant CVRFs, which determined a poorer cardiovascular risk profile in comparison with men, as well as a higher rate of major amputation.

In this study, in addition to diabetes, two other CVRFs, hypertension and obesity, had a significantly higher prevalence in the female gender.

In the case of hypertension and metabolism-related CVRFs, something similar occurs when differentiating between genders, since the percentage of female amputees who are hypertensive, obese or have dyslipidemia is higher than that of males.

Published studies affirm that menopausal status and associated obesity is the main predictor of metabolic alterations associated with cardiovascular risk in menopausal women, with an increase in anthropometric parameters and plasma lipid indices being observed in postmenopausal women, closely related to age increase²⁴⁻²⁷. According to these studies' conclusions, women suffer a change in lipid profile since menopause, mainly due to estrogen deficit, which generates higher susceptibility to cardiovascular diseases, which is consistent with the results of our study, in which there was a higher prevalence of obesity and dyslipidemia in females.

Smoking was the only CVRF that was more prevalent in males. This risk factor is regarded by some authors^{28,29} as a fundamental CVRF for preventable

peripheral arterial disease. LL amputations in patients with peripheral arterial disease who smoke are twice than those recorded in never-smokers. The higher prevalence of smoking in male patients in this study could explain the large difference in the percentage of amputations performed according to gender, since the percentage of male amputees was three times that of women.

Considering that the cardiovascular risk profile of women in this study was clearly more unfavorable, except for smoking, it would be expected for the female gender to have the highest prevalence of LL amputations, but only one third of amputees in the sample are women.

Most amputee women were of advanced age, which entails for them cessation of ovarian steroidogenesis and, therefore, of the protection it generates at younger ages, which favors the development of some modifiable CVRFs such as diabetes, hypertension, dyslipidemia and obesity. For some authors^{30,31}, age increase would determine an increase in anthropometric parameters and plasma lipid indices in postmenopausal women, with this demographic variable, and along with it menopause, in which there is a higher propensity to accumulate CVRFs, turning into an essential factor for the development of peripheral vascular pathology in the female gender.

This work demonstrated the association between the female gender, advanced age and three CVRFs (diabetes, hypertension and obesity), which would confirm the relationship between age increase in women and the presence of a poorer cardiovascular profile.

However, and without neglecting to point out the important role age plays in cardiovascular risk profile, we cannot affirm that the results of this study, with a more unfavorable female cardiovascular risk profile and higher prevalence of amputation in this gender, are entirely caused by older age in the group of women. LL amputation in female patients of this study occurred in poorer vascular conditions than in men, at older ages and with a more unfavorable cardiovascular risk profile at the time of surgical intervention.

Age might be regarded as a necessary, but not sufficient condition for the occurrence and progression of atherosclerotic lesion, which in most cases is the cause of LL amputation, since although amputee women were older and had a poorer clinical profile, the male gender was the most affected by this type of surgery.

In this study, the female gender was also related to a higher level of LL amputation, since they underwent major amputation more often than men, with the importance the level at which this type of surgery is performed has for the evolution, prognosis and quality of life of patients.

Conclusions

This study confirms the important role of gender as a risk factor to be considered in LL amputation for non-traumatic causes, given that gender determines a more unfavorable cardiovascular risk profile in women with vascular pathology who undergo amputation. A negative association with three CVRFs (diabetes, hypertension and obesity) was also demonstrated in women, as well as a higher predisposition to suffer major amputation.

The results of this work, together with the evidence generated by clinical practice and the considerable gap in the knowledge of the specific clinical profile of LL amputee female patients, make it expedient to design new multicenter studies, with larger inclusion of women in the sample in order to definitively establish differential parameters according to patient gender, to the biological mechanisms involved and their level of influence on this radical surgery, which shows a worrying growing trend.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments have been performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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