

Diabetic foot in Mexico: risk factors for mortality after a major amputation, at 5 years, in a second-level public health hospital

Pie diabético en México: factores de riesgo para mortalidad posterior a una amputación mayor, a 5 años, en un hospital de salud pública de segundo nivel

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Abstract

Objective: To investigate retrospectively at 5 years the mortality rate in postoperative patients of major amputation secondary to diabetic foot and to identify the associated risk factors that increase mortality in the Mexican population. **Method:** Retrospective study that included patients who underwent major amputation secondary to diabetic foot from January 1 to December 31, 2009 in a second-level hospital. **Results:** 37 patients who met the inclusion criteria were included in the study protocol, finding that 10 patients (27.03%) were still alive and 27 patients (72.97%) had died. Observing In patients who undergo an amputation and have three or more comorbidities, they have a 1.6 times higher risk of dying ($p = 0.018$) and that the higher the glycemia prior to the amputation, the greater the probability of dying at 5 years ($p = 0.015$). **Conclusions:** Studies are needed in Mexico with prospective follow-up, multicenter in nature, with a heterogeneous sample, which allows us to have a National panorama.

Keywords: Infracondylar amputation. Supracondylar amputation. Mortality in major amputation. Diabetic foot.

Resumen

Objetivo: Investigar de manera retrospectiva a 5 años el porcentaje de mortalidad en los pacientes operados de amputación mayor por pie diabético e identificar los factores de riesgo asociados que aumentan la mortalidad en la población mexicana. **Método:** Estudio retrospectivo de pacientes sometidos a amputación mayor por pie diabético del 1 de enero al 31 de diciembre de 2009 en un hospital de segundo nivel. **Resultados:** Se incluyeron en el protocolo de estudio 37 pacientes que cumplían los criterios de inclusión, y se encontró que 10 (27.03%) continuaban con vida y 27 (72.97%) habían fallecido. Los pacientes a quienes se realizó una amputación y tenían tres o más enfermedades concomitantes mostraron un riesgo 1.6 veces más alto de morir ($p = 0.018$). Cuanto mayor era la glucemia previa al momento de la amputación, mayor fue la probabilidad de muerte a 5 años ($p = 0.015$). **Conclusiones:** En México hacen falta estudios con seguimiento prospectivo, de carácter multicéntrico, con una muestra heterogénea, que permitan tener un panorama nacional.

Palabras clave: Amputación infracondílea. Amputación supracondílea. Mortalidad en amputación mayor. Pie diabético.

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Date of reception: 21-03-2020

Date of acceptance: 12-09-2020

DOI: 10.24875/CIRUE.M20000319

Cir Cir (Eng). 2021;89(3):279-284

Contents available at PubMed

www.cirugiaycirujanos.com

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Introduction

Diabetic foot is a complication of diabetes associated with high morbidity, elevated mortality, high costs and reduced quality of life. It usually occurs as diabetic foot ulcers with or without an underlying infectious process and Charcot's foot in the presence of peripheral neuropathy or peripheral arterial disease in people with diabetes¹, and is the most important precursor for lower extremity amputations^{1,2}. Diabetic foot disease overall prevalence is estimated to be around 6%^{1,3}. A population-based cohort study in the United Kingdom showed that the development of a diabetic foot ulcer is associated with a mortality rate of 5% in the first 12 months and 42% at 5 years; furthermore, these patients have a 2.5-fold higher risk of death than diabetic patients without foot injuries. Older age, the male gender, and smoking⁴⁻⁶ have been described as risk factors. A diabetic patient has a risk of amputation 15 to 40 times higher than an individual who is not diabetic⁷.

The rates of lower extremity amputations secondary to diabetic foot were 8.3, 9.5, and 9.2 per 100,000 in the general population in Mexico in the years 2009, 2010 and 2011, respectively⁸.

In many cases, it is difficult to choose the level of amputation, which is important for the recovery of the amputated limb since, in general, these patients are difficult to rehabilitate and also suffer significant mortality associated with medical problems that often precede definitive healing of the wound. When an infracondylar amputation is carried out, up to 75% of older patients have been observed to never be able to ambulate again and to have further healing problems that require conversion to supracondylar amputation in an additional 20% of patients⁹.

Thirty-day mortality after amputation in patients with diabetic foot and type 2 diabetes mellitus is 8.6%, between 13% and 40% at 1 year, 35% to 65% at 3 years, and 39% to 80% at 5 years, with these figures being worse than for most malignant tumors^{7,10,11}. These percentages may increase in developing countries, since patients tend to seek medical care when the ulcer infection is advanced, which increases the risk of amputation and death¹⁰.

In addition to age (hazard ratio [HR] per year: 1.08), the male gender (HR: 1.65; 95% confidence interval [CI]: 1.18-2.32; $p = 0.004$), chronic kidney disease (HR: 1.83), dialysis (HR: 6.43) and peripheral arterial

disease (HR: 1.44) are independent variables predictive of death^{6,12}.

Patients with end-stage renal disease receiving dialysis have an especially high risk of amputation, with one study having found that, in 2014, 2.66% (95% CI: 2.59-2.72) of these patients underwent amputations¹³. One-year adjusted lower extremity amputation mortality rates for patients with end-stage renal disease who receive dialysis decreased from 52.2% (95% CI: 50.9-53.4) in 2000 to 43.6% (95% CI: 42.5-44.8) in 2013¹³. Another study found that early postoperative in-hospital mortality in amputation-operated patients who were on dialysis was higher (7.7% vs. 2.9%; $p < 0.001$), and myocardial infarction events were marginally higher (2.4% vs. 1.6%; $p = 0.053$) than in patients not on dialysis¹⁴.

In another study, 39.7% of patients had supracondylar amputation and 61.1% of them died. These patients showed a 4.5-fold higher risk of death than patients who had amputations at other levels⁷.

More than 50% of patients undergoing a first major amputation have evidence of peripheral arterial disease⁶.

Faglia et al.⁵ found that the female gender was independently associated with death (HR: 1.96; 95% CI: 1.08-3.56; $p = 0.027$). In developed countries, more than half post-amputation deaths are caused by cardiovascular and cerebrovascular events. In contrast, studies on mortality in amputated patients with diabetic foot in developing and newly developed countries report a much higher proportion of deaths from septic complications⁶.

A 2017 meta-analysis found that clinical risk factors associated with higher mortality included type 2 diabetes mellitus (odds ratio [OR]: 2.02-2.20), peripheral arterial disease (OR: 2.34), coronary artery disease (OR: 2.01-3.33), cerebrovascular disease (OR: 2.50-2.55), end-stage renal disease and dialysis dependence (OR: 2.12-5.35), American Society of Anesthesiologists (ASA) class ≥ 4 (OR: 2.04), dementia (OR: 2.02-2.77), and non-ambulatory status (OR: 2.28). Surgical factors, including a higher amputation level (OR: 2.4-3.2) and the need for staged surgery with initial major amputation (OR: 2.49), were also correlated with higher mortality¹⁵. Factors independently associated with death were older age (OR: 1.29), history of heart failure (OR: 1.71), kidney disease (OR: 1.84), and chronic obstructive pulmonary disease (COPD) (OR: 1.3)¹⁵.

In another study, lack of prosthesis creation was an independent factor of mortality (OR: 2.60; 95% CI: 1.16-6.25; $p = 0.028$)⁵.

Long-term data on mortality of patients operated on for major amputation secondary to diabetic foot in Mexico are scarce⁸. Studies that look for more detailed information on clinical and surgical conditions, specific causes of mortality and indirect costs are urgently needed in order to improve understanding on the mortality and economic burden of this diabetes complication in the country⁸.

The main purpose of our study was to retrospectively investigate the 5-year mortality rate in patients with type 2 diabetes mellitus undergoing major amputation secondary to diabetic foot, and the secondary objective was to identify associated risk factors that increase mortality in the Mexican population.

Method

The retrospective cohort consisted of all subjects who underwent major amputation secondary to diabetic foot from January 1, 2009, to December 31, 2009 at Zone No. 6 General Hospital of Monterrey, Nuevo León, Mexico. The patients were identified on the major amputation registry of the hospital chronic wound program, with all those who had a complete medical record and who had type 2 diabetes mellitus according to patient chart being included in the study and, in case of not having a death certificate in the medical records of the clinic they belonged to or at the hospital itself, subjects had to be able to be located at their home or through a relative who attested that the patient was still alive. The study was reviewed and approved by the Ethics Committee of Zone No. 6 General Hospital, and informed consent was obtained from all the relatives of patients at the time of the survey, with the totality of patients' homes being visited, and those who were not localizable being discarded by convenience. Data were collected on whether or not the patient was still alive, age at the time of amputation, gender, the clinic the subject belonged to, months of survival after amputation, etiology of death obtained from the death certificate and of the amputation obtained from the medical record, type of amputation, whether the subject was affiliated to the ATHODO IMSS program (which provides home health care), time from disease diagnosis to amputation, last capillary glucose report recorded on patient chart prior to amputation, comorbidity obtained from the medical record, whether or not the subject had a record of wound dressings, whether or not the subject followed a diabetic diet, and whether the subject had previous major amputation of the contralateral limb.

After the information was collected, the database was anonymized and exported to a statistical software.

Median and interquartile range were used for non-normally distributed continuous variables; mean and standard deviation for normally-distributed continuous variables; and percentage for discrete variables. Discrete variables were analyzed with the chi-square test and, when appropriate, with Fisher's exact test, and non-normally distributed quantitative variables, using nonparametric Mann-Whitney's U-test. A multivariate analysis was carried out to identify independent predictors of perioperative mortality with logistic regression analysis. ORs and 95% CIs were estimated, and a p-value < 0.05 was established as the threshold for statistical significance. Statistical analysis was carried out with the SPSS program, version 25 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Of the 66 patients who belonged to the amputation program in 2009, 37 who met the inclusion criteria were included in the study protocol. Among these 37 patients, 10 (27.03%) were found to be still alive and 27 (72.97%) had died. Of the totality of patients, 25 were males, out of whom 18 (72%) had died (OR: 1.16), and 12 were females, out of whom 9 (75%) had died (OR: 1.05) (Table 1).

Mortality according to the number of years after amputation was 8.1% before the first year, 16.2% before the second, 18.9% before the third, 18.9% before the fourth and 10.8% before the fifth year; and, added together, it was 8.1% before the first year, 43% at 3 years and 72.97% at 5 years.

In the 27 patients who died, the causes of death, in order of frequency, were septic shock in 12, ischemic heart disease in 3, diabetes decompensation in 8, chronic kidney disease in 3, and cerebrovascular disease in 1 patient.

Regarding the reason for amputation, 20 patients who underwent amputation due to infectious etiology (83.3%; OR: 2.3; p = 0.118), 21 patients with vascular etiology (67.7%; OR: 1.28; p 0.162) and 8 patients with neuropathic etiology were found to have died (61.5%; OR: 0.711; p = 0.275).

When the relationship between the type of amputation and patient death was analyzed, among those with supracondylar amputation, 25 (73.5%; OR: 0.72) were found to have died, and among those with infracondylar amputation, 2 had died (66.7%; p = 0.275).

Table 1. Population characteristics

Variable		Alive	Dead	Alive OR	Dead OR	p- value
Gender	Males	7 (28.0%)	18 (72.0%)		1.16	
	Females	3 (25%)	9 (75%)		1.05	
Etiology	Infectious	4 (16.7%)	20 (83.3%)	0.54	2.3	0.118
	Vascular	10 (32.3%)	21 (67.7%)		1.2867	0.162
	Neuropathic	5 (38.5%)	8 (61.5%)	1.68	0.711	0.275
Type to amputation	Supracondylar	9 (26.5%)	25 (73.5%)		1.35	0.275
	Infracondylar	1 (33.3%)	2 (66.7%)		0.72	
Comorbidities						
HT	With HT	8 (29.6%)	19 (70.4%)	1.13	0.675	0.694
	Without HT	2 (20%)	8 (80%)			
CKD	With CKD	4 (20%)	16 (80%)	0.675	0.297	0.46
	Without CKD	6 (35.3)	11 (64.7)			
AF	With AF	0 (0%)	1 (100%)		1.038	1
	Without AF	10 (27.2%)	26 (72.2%)			
CHF	With CHF	0 (0%)	8 (100%)		1.421	0.79
	Without CHF	10 (34.5%)	19 (65.5%)			
CVE	With CVE	0 (0%)	2 (100%)		1.08	1
	Without CVE	10 (28.6%)	25 (71.4%)			
COPD	With COPD	0 (0%)	3 (100%)		1.125	0.54
	Without COPD	10 (29.48%)	24 (70.6%)			
AMI	With AMI	1 (11.1%)	8 (88.9%)	0.338	1.279	0.393
	Without AMI	9 (32.1%)	19 (67.9%)			
3 or more comorbidities	More than 3	0 (0%)	11 (100%)		1.688	0.018
	Less than 3	10 (38.5%)	16 (61.5%)			
PREV AMP	Yes	0 (0%)	7 (100%)		1.35	0.155
	No	10 (33.3%)	20 (66.7%)			

Nominal variables are expressed as total frequency (%) and normally-distributed quantitative variables as the mean $\pm$ standard deviation.

AF: atrial fibrillation; AMI: acute myocardial infarction; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVE: cerebrovascular event; HT: hypertension; OR: odds ratio; PREV AMP: Previous major amputation of contralateral leg.

When the role of comorbidity was analyzed, 19 patients (70.4%; OR: 0.675; $p = 0.694$) were found to have died with hypertension; 16 patients (80%; OR: 1.47), with chronic kidney disease; one patient, with atrial fibrillation (OR: 1.038; $p = 1$); 8 patients with heart failure (OR: 1.421; $p = 0.79$), 2 patients with cerebrovascular disease (OR: 1.08; $p = 1.0$), 3 patients with COPD (OR: 1.125; $p = 0.54$); and 8 patients (88.9%; OR: 1,279; $p = 0.39$) with acute myocardial infarction.

When patients with three or more comorbidities were specifically searched and related to alive and dead patients, no patient (0%) with more than three concomitant diseases was found to be still alive and all 11 (100%) had died, whereas among those with less than three concomitant diseases, 10 patients (38.5%) were found to be still alive and 16 (61.5%)

were dead. Fisher's exact test showed statistical significance for deceased patients ($p = 0.018$; OR: 1.688).

None of the seven patients with bilateral major amputation was still alive (OR: 1.35; $p = 0.15$).

Last blood glucose prior to amputation was analyzed in alive and dead patients, and the higher the blood glucose at the time of amputation, the probability of death at 5 years was found to be higher ($p = 0.015$). Therefore, a receiver operating characteristic (ROC) curve was generated in order to find out from which blood glucose threshold value at the time of amputation patients have the highest risk of death at 5 years, with the most sensitive result being 134 mg/dL (sensitivity of 96% and specificity of 10%); the best relationship between sensitivity and specificity was observed for 170 mg/dL (sensitivity of 92% and specificity of 40%) and 190 mg/dL (sensitivity of 70%

Table 2. Receiver operating characteristic (ROC) curve coordinates and last blood glucose value prior to amputation

Last blood glucose (mg/dL)	Sensitivity	1-specificity
107	1	1
134	0.963	0.9
165	0.926	0.7
170.5	0.926	0.6
175.5	0.889	0.6
190	0.704	0.4
205	0.519	0.3
211	0.444	0.3
213.5	0.407	0.3
217.5	0.37	0.3
230	0.37	0.2
245	0.37	0.1
265	0.296	0
280.5	0.259	0
299	0.222	0
319.5	0.185	0
326.5	0.148	0
390.5	0.111	0
452.5	0.074	0
477.5	0.037	0
501	0	0

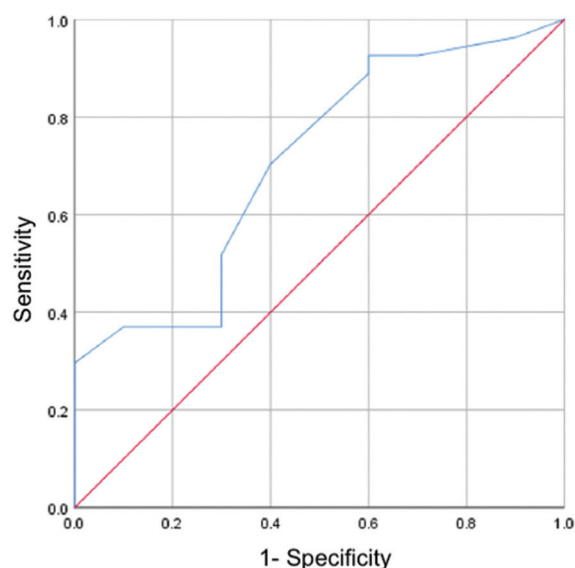
and specificity of 60%), and the highest specificity was observed for 265 mg/dL (sensitivity of 29% and specificity of 100%) (Table 2) (Fig. 1).

Discussion

In our study, 1-year mortality was 8.1%, which is lower than that reported in the literature (13-40%); at 3 years, it was 43%, which is consistent with that reported in the literature (35-65%); and at 5 years, it was 72.97%, which also agrees with that reported in the literature (39-80%)^{7,10,11}.

Among the patients with supracondylar amputation, 73% were found to have died (OR: 0.72; $p = 0.275$); the literature describes a risk of 61.1% (OR: 4.5) vs. patients with amputation at other levels⁷.

The reason for amputation in the 37 patients of our study was infectious etiology in 24, vascular etiology

**Figure 1.** Receiver operating characteristic (ROC) curve for mortality vs. last blood glucose obtained prior to amputation. Diagonal segments are generated by ties. Area under the curve = 0.707.

in 31 and neuropathic etiology in 13, which is consistent with the literature, which refers that more than 50% of patients who experience a first amputation show evidence of peripheral arterial disease⁶.

Heart failure entailed an increase in the risk of death of 1.42 ($p = 0.79$), which is consistent with reports in the literature, which indicate an increase in the risk of death 1.71 times higher than in patients without heart failure¹⁵.

Of the patients with chronic kidney disease in our study, 80% died (OR: 1.47; $p = 0.46$), which is not consistent with the literature, where 43.6% are reported to die (OR: 1.84); this, because those studies did not take into account if the patient was on some type of renal replacement therapy^{14,15}.

A risk increase was observed in patients with COPD, 1.125 times higher than in the population without COPD, which is consistent with the literature, which reports a 1.3-fold higher risk.

In our study, acute myocardial infarction entails a 1.2-fold higher risk than in patients without infarction, while the literature reports a risk increase in patients with infarction 2.01-3.33 times higher than in patients without infarction.

No studies have been found referring a specific number of concomitant diseases associated with amputation that increase the risk of death; in our study, we found that three or more diseases are associated

with a 1.6-fold increase in the risk of death in comparison with patients who have two or fewer concomitant diseases ($p = 0.018$).

Finally, in the case of blood glucose determined prior to amputation, the higher it was, the probability of death at 5 years was shown to be higher ($p = 0.015$), and the probability of dying within 5 years after amputation when having a blood glucose of 134 mg/dL was 10%; with blood glucose of 170 mg/dL, it was 40%; with a blood glucose of 190 mg/dL, it was 60%; and with a blood glucose of 265 mg/dL, it was 100%.

In our study, the most common cause of death was septic shock, in 12 patients, similar to findings reported in developing countries⁶.

Conclusions

The higher the blood glucose level at the time of amputation, the higher the probability of death at 5 years, with the risk of death being 1.6 times higher in patients with three or more concomitant diseases. Within the world literature, there are multiple studies carried out in the United States of America and in Europe, but there is a need in Mexico for studies with prospective follow-up, multicenter in nature and with heterogeneous samples that allow having a national outlook.

Acknowledgements

To Zone No. 6 General Hospital, for allowing us to use the resources for the preparation of this article for educational purposes.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were 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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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