

# Incidence of major amputations secondary to diabetic foot prior and after endovascular revascularization

## Incidencia de amputaciones mayores secundarias a pie diabético antes y después revascularización endovascular

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### Abstract

**Objective:** The objective of the study was to compare the incidence of major amputation of the lower limbs secondary to the diabetic foot (DF) before and after the introduction of endovascular therapy as a method of revascularization in patients with severe ischemia. **Methods:** This retrospective, observational, and longitudinal study evaluated patients diagnosed with DF from June 2012 to June 2019. The incidence of major amputation was compared with prior endovascular revascularization and subsequent use 2016 as the reference year. We compared the higher amputation rates between the two time periods using the Chi-square test at a significance level of 0.05. **Results:** A total of 860 patients, 218 (60%) underwent endovascular revascularization. The absolute risk of major amputation was 56% (95% confidence interval [CI], 0.50-0.52; odds ratio [OR], 1.29) in the first period of time and 19% (95% CI, 0.16-0.23; OR, 0.24) in the second period of time, with an OR of 0.19 (95% CI, 0.14-0.26), relative risk of 0.33, risk reduction relative of 0.66, and risk difference of 0.37. The difference in the incidence of major amputation between the two time distances was statistically significant. **Conclusions:** The incidence of PD is increasing overtime. Revascularization through an endovascular approach may be a feasible alternative to reduce significant amputation rates, even in countries with a high incidence of diabetes. However, more studies are required to support these conclusions.

**Key words:** Diabetic foot. Limb treating chronic limb ischemia. Major amputation. Endovascular revascularization.

### Resumen

**Objetivo:** Comparar la incidencia de amputaciones mayores de miembros inferiores secundaria al pie diabético (PD) antes y después de la introducción de la terapia endovascular como método de revascularización en pacientes con isquemia severa. **Métodos:** Estudio retrospectivo, observacional y longitudinal que evaluó a pacientes diagnosticados con PD desde junio de 2012 hasta junio de 2019. La incidencia de amputación mayor se comparó con la revascularización endovascular previa y posterior utilizando 2016 como año de referencia. Comparamos las tasas de amputación mayor entre los 2 períodos de tiempo usando la prueba de chi-cuadrado a un nivel de significancia de 0.05. **Resultados:** Un total de 860 pacientes. 218 (60%) se sometieron a revascularización endovascular. El riesgo absoluto de amputación mayor fue del 56% (intervalo de confianza del 95% [IC 95%]: 0,50-0,52; odds ratio [OR]: 1,29) en el primer período de tiempo y del 19% (IC 95%: 0,16-0,23; OR: 0,24) en el

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segundo período de tiempo, con un OR de 0.19 (IC 95%: 0.14-0.26), riesgo relativo de 0.33, reducción del riesgo relativo de 0.66 y diferencia de riesgo de 0.37. La diferencia en la incidencia de amputación mayor entre los 2 períodos de tiempo fue estadísticamente significativa. **Conclusiones:** La incidencia de PD está aumentando con el tiempo. La revascularización mediante un enfoque endovascular puede ser una alternativa factible para reducir las tasas de amputación importantes incluso en países con alta incidencia de diabetes. Sin embargo, se requieren más estudios para apoyar estas conclusiones.

**Palabras clave:** Pie diabético. Isquemia crónica de extremidades. Amputación mayor. Revascularización endovascular.

## Introduction

Diabetic foot (DF) is one of the most common complications of diabetes mellitus (DM), which can lead to major amputation of the lower limb with a considerable disabling impact. Patients with DM have 25% risk to develop foot ulcers in their entire life. Among patients with diabetic foot ulcers, 20% undergo major amputation, and there is 50% mortality rate from cardiovascular complications at 5 years; therefore, the prognosis is similar to that of pancreatic cancer or lymphoma<sup>1</sup>. It is reported that 75 people are amputated per day in Mexico, in some regions of the world, an amputation secondary to DM complications is performed every 20 s. Major amputation (above and below the knee) is highly disabling and increases long-term health-care costs<sup>2,3</sup>.

It has been reported that up to 60% of patients with DF have atherosclerosis in the lower limbs being infragenicular arteries the most affected vessels<sup>4</sup>. In addition to hyperglycemia, DM is associated with dyslipidemia and vascular inflammation, resulting in structural disorders of the vascular wall, smooth muscle cell alteration, and endothelial injury<sup>5</sup>. In addition, infection in patients with DM may increase the oxygen need and tissue perfusion to feet due to increased metabolic activity and concomitant thrombosis of small vessels<sup>6</sup>. Moreover, the ischemia processes increase the severity of infection and increase the risk of major amputations. Therefore, revascularization should be indicated immediately in advanced stages of peripheral arterial disease (PAD) in DF scenario<sup>7,8</sup>. Open surgery procedures are revascularization options in patients with good cardiac function, but on the other hand, endovascular procedures are safer in cases of cardiac dysfunction<sup>9</sup>. Minimal invasive approaches have gained popularity in recent years because they reduce patient recovery time, in some centers of the United States, mayor amputation incidence was 35% in 1990, when surgical revascularization was a predominant option, but decreased to 6% in 2010, when minimally invasive procedures were the revascularization option in 89% of cases<sup>7,10</sup>.

Few studies have evaluated amputation rates secondary to DF in developing countries with high incidence

of diabetes. In Mexico, 10.4% of the population had diabetes in 2016, Mexican population also has one of the highest rates of deaths attributable to diabetes and disability-adjusted life-years<sup>11</sup>. From 2004 to 2005, hospital admissions due to DF increased in Mexico by 10% and the rate of major amputation increased by 4%<sup>12</sup>. Data from the National Health and Nutrition Survey (Encuesta Nacional de Salud y Nutrición – ENSANUT) indicated that from 2004 to 2013, the increased incidence of DF was 7.5%<sup>3</sup>. Otherwise, the role of endovascular interventions to reduce the incidence of major amputations is still unknown in Latin American population and actually, we are going through financial cuts to health system, for this reason, all strategies that have already proven effective decreasing major amputations in other countries must be implemented and promoted in the Mexican population<sup>13</sup>. The aim of this study was to determine the incidence of lower limb major amputation in patients with DM admitted in a single center from June 2012 to June 2019 and compare the incidence of major amputations during the period starting 3.5 years prior and 3.5 years subsequent to the introduction of endovascular therapy as a revascularization in severe ischemia cases of DF.

## Methods

This retrospective, observational, and longitudinal study was conducted at Hospital Regional Lic. Adolfo López Mateos of the ISSSTE in Mexico City, data from patients diagnosed with DF (defined according to the World Health Organization [WHO] guidelines<sup>14</sup>) admitted to the vascular surgery division from June 2012 to June 2019 were collected and analyzed. The presence of ulcers, ulcer depth, and gangrene was evaluated using the Wagner classification and the Wound, Ischemia, and foot infection (WIFI) grading system<sup>6</sup>. The clinical stage of PAD was also evaluated according to the Rutherford classification (only Stages V and VI were considered).

Demographic data, comorbidities, and risk factors (type of diabetes, high blood pressure, history of smoking, and renal replacement therapy in patients with

**Table 1.** Demographic data and comorbidities in the study population

Variable	Total number of patients n = 860 (% or SD)	Patients admitted from 2012 to 2015 n = 284 (% or SD)	Patients admitted from 2016 to 2019 n = 576 (% or SD)	p-value
Men	603 (70)	202 (71)	401 (69)	NS
Women	257 (30)	82 (29)	175 (31)	NS
Average age	66 (11)	66 (10)	66 (11)	NS
Wagner I	7 (1)	5 (2)	2 (1)	NS
Wagner II	36 (8)	7 (4)	29 (10)	NS
Wagner III	262 (60)	99 (57)	165 (61)	NS
Wagner IV	441 (16)	128 (23)	313 (12)	< 0.05
Wagner V	114 (13)	45 (12)	69 (13)	NS
Peripheral arterial disease	424 (49)	112 (39)	312 (50)	< 0.05
Rutherford V	368 (42)	88 (30)	280 (48)	< 0.05
Rutherford VI	56 (6)	24 (8)	32 (5)	NS
Renal replacement therapy in patients with CKD	67 (7)	30 (10)	37 (6)	NS
Previous smokers	457 (53)	164 (57)	293 (50)	NS
Active smokers	160 (18)	49 (17)	111 (19)	NS

CKD: chronic kidney disease, NS: not significant.

chronic kidney disease) were analyzed. The primary outcome was major amputation. Amputation above and below the knee was considered major, whereas transmetatarsal and toe amputations were considered minor. The lower limb was preserved in patients with complete wound healing. The incidence of major amputation before and after endovascular revascularization was compared using the year 2016 as the benchmark year because in January 2016, a facility for endovascular suite was set up at our center to perform minimally invasive revascularization procedures. The following two time periods were compared: first period from June 30, 2012 to December 31, 2015, when we first began performing open revascularization in our department; the second period from January 1, 2016 to June 1, 2019, when we first began performing endovascular revascularization.

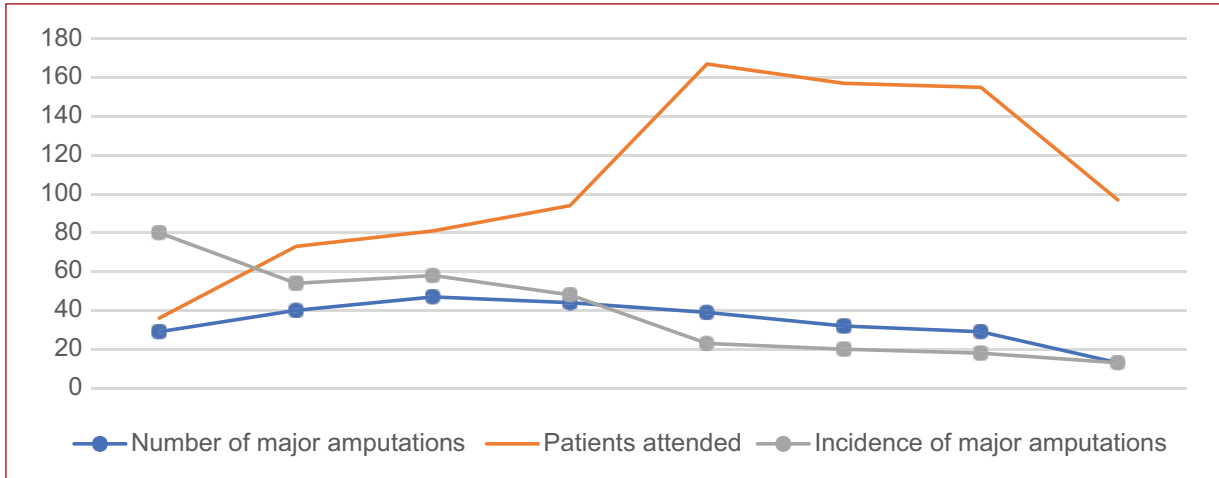
Demographic and clinical data were analyzed descriptively, tabulated, converted to percentages, and reflected in central tendency measures. The two time periods were compared using the Student's t-test for continuous variables and comparison of medians for categorical variables. The Chi-square test was used to compare the rates of major amputation between the two time points, and  $p < 0.05$  was considered statistically significant. SPSS software version 25.0 was used for data

processing and inferential statistics. The study was granted ethical approval by the Clinical Research and Ethics Committee of the "Hospital regional Lic. Adolfo López Mateos (ISSSTE)" in March 2019, with institutional number 029-2019. Informed consent was not required.

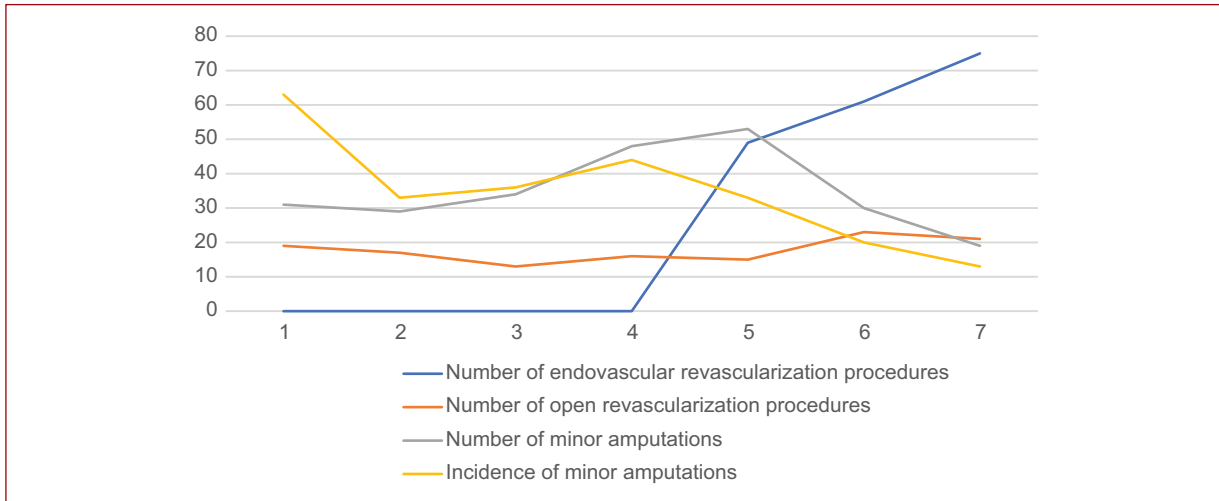
## Results

A total of 860 patients diagnosed with DF from June 2016 to June 2019, with a mean age of  $66 \pm 11$  years, were included in the study, 70% of our study population were male. Demographic data and comorbidities are described in [table 1](#).

A total of 424 patients were diagnosed with concomitant PAD (Rutherford Stages V and VI, WIFI Stages III and IV). Meanwhile, 359 patients underwent lower limb revascularization, 218 (60 %) underwent endovascular revascularization, and 141 (40%) underwent open revascularization ([Fig. 1](#)). During the study period (2012-2019), 273 patients underwent major amputation (31.7%) and 265 (30%) had minor amputation ([Fig. 2](#)). A total of 160 major amputations (59%) were performed from 2012 to 2016 and 113 (41%) major amputations correspond to after "endo-first approach" period. The incidence or absolute risk of major amputation was 56% (95% confidence interval (CI) [95%



**Figure 1.** Distribution of patients with diabetic foot admitted to the Regional Hospital “Lic. Adolfo López Mateos” in Mexico City, Mexico, from 2012 to 2018.



**Figure 2.** Distribution of revascularization procedures and minor amputations in patients with diabetic foot admitted to the Regional Hospital “Lic. Adolfo López Mateos” in Mexico City, Mexico, from 2012 to 2018.

CI], 0.50-0.52; OR, 1.29) in the first period (2012-2015) and 19% (95% CI, 0.16-0.23; OR, 0.24) in the second period (2016-2019), with an OR of 0.19 (95% CI, 0.14-0.26), relative risk (RR) of 0.33, reduction in RR of 0.66, risk difference of 0.37, and number needed to treat of 2.7 (95% CI, 2.3-3.3). The difference in incidence between the two periods was statistically significant ( $p < 0.05$ ). The number of procedures and the incidence of major and minor amputations per year are shown in [table 2](#).

Endovascular revascularization began in 2016, with 218 procedures performed until July 1, 2019, and the rate of open procedures decreased from 100% in 2012 to 26.6% in 2019. There were no significant differences

in the average number of open revascularization procedures between the two time periods.

## Discussion

The prevalence of amputation was significantly different between periods analyzed in our study, in other words, before and after implementation of “endo-first approach” to perform revascularization procedures in DF patients. These findings are relevant for us because the quality standards in health care of the Organization for Economic Cooperation and Development (OECD, Mexico is a member) consider major amputation as an indicator of the quality of care

**Table 2.** Number and percentage of vascular procedures performed between 2012 and 2019 in the Regional Hospital “Lic. Adolfo López Mateos” in patients who underwent amputation

	2012 (n = 36)	2013 (n = 73)	2014 (n = 81)	2015 (n = 94)	2016 (n = 167)	2017 (n = 157)	2018 (n = 155)	2019 (n = 97)
Endovascular revascularization, n = 218 (%)	0	0	0	0	49 (76)	61 (72)	75 (78)	33 (66)
Open revascularization, n = 141 (%)	19 (100)	17 (100)	13 (100)	16 (100)	15 (23)	23 (27)	21 (21)	17 (34)
Major amputation, n = 273 (%)	29 (10)	40 (15)	47 (18)	44 (17)	39 (14)	32 (11)	29 (10)	13 (4)
Incidence of major amputations, n = 314 (%)	80 (28)	54 (19)	58 (20)	48 (16)	23 (3.9)	20 (3.4)	18 (3)	13 (2.2)
Minor amputations, n = 265 (%)	31 (12)	29 (11)	34 (13)	48 (18)	53 (20)	30 (11)	19 (7)	21 (8)
Incidence of minor amputations, n = 267 (%)	63 (22)	33 (11)	36 (12)	44 (15)	33 (5)	20 (3)	13 (2)	25 (4)

of DM of health institutions<sup>15</sup>. Complications secondary to DM represent 87% of treatment costs of the entire disease, major amputation is a disabling complication of DM associated with increased long-term health-care costs; indeed, an amputation performed in our country in 2013 cost approximately \$ 5000.00 USD. Because direct costs of DF represent 10% of the total grant of diabetes care<sup>12</sup>, indirect costs (i.e., from premature death, absenteeism, and disability) are substantial too. Furthermore, the total treatment cost of DF exceeded that cardiovascular treatment of complications due to DM. Accordingly, to reduce the rate of major amputation is a feasible approach to decrease the burden of DF, improve the quality of life of patients, and decrease health care costs<sup>16</sup>.

It should be noted that revascularization by itself does not decrease the rate of amputation, the set of increased understanding of the DF pathophysiology, as well as advances in endovascular diagnostic and treatment techniques, stratification tools, and the development of treatment guidelines could be other causal factors. Indeed, advances in diagnostic techniques in particular help determine the status of DF-related complications before and after the initiation of endovascular therapies, thereby helping to determine future strategies, identify cost-effective tools, and optimize clinical outcomes<sup>17</sup>. There is little evidence supporting the hypothesis that revascularization is superior in reducing the number of amputations when compared to the following: risk detection and stratification, timely patient referral, patient education, and multidisciplinary care. However, the results of revascularization procedures are promising mainly in countries where prevention has not been incentivized and where the patients seek for specialized medical attention in advanced stages of the disease<sup>18</sup>.

The number of patients with DF admitted to our department increased, and this phenomenon is

comparable to results from international studies, as a meta-analysis performed in 2011 reported that the rate of major amputation varied from 3.6 to 68.4/1,000,000 year worldwide<sup>19</sup>. Moreover, the number of patients with DF admitted to our center has increased almost 2-fold from 2012 to 2018, with an associated increase in health-care costs. According to the data of the Mexican Health Foundation FUN-SALUD, the cost of care of DM and its complications represented 2.2% and 2.6% of the national gross domestic product in 2012 and 2018, respectively. Continued increased costs could be catastrophic for health systems in general<sup>20</sup>.

Compared to other statistical data from Mexico reported in 2013 by the Mexican Social Security Institute (Instituto Mexicano del Seguro Social – IMSS), in Southern Mexico City, there were 187 major amputations and 166 minor amputations in 1 year, which is a 5-fold increase relative to the number of procedures performed at our hospital. These results are comparable to the percentage of the population being assisted by the IMSS since it is estimated that 6 in 10 Mexicans receive health-care services from this institute<sup>12</sup>. Therefore, the increase in DF, major amputation, and the cost of diabetes care are a worldwide trend and not exclusive to our center, and comprehensive measures are crucial to counteract this increase.

Regarding demographic data, age is a risk factor that increased the prevalence and incidence of PAD by more than 10%, especially in the 60-70 years age group. The mean age in our sample was 66 years<sup>21</sup>. The rate of smoking and its complications has decreased in developed countries. However, this trend was not observed in our sample since 53% of our patient population that were submitted for amputation had a history of smoking. Furthermore, 21% increase in the amputation rate has been verified in current smokers<sup>22</sup>.



Since 2005, the WHO and the International Diabetes Federation have reported that 80% of diabetes-related amputations are preventable<sup>14</sup>. Therefore, efforts should be directed to reduce the risk factors and complications and provide revascularization (open or endovascular) treatment options for high-risk patients (those with perioperative mortality > 5% or 2-year survival < 50%)<sup>5</sup>. Endovascular revascularization may be the treatment of choice to prevent amputation and has decreased the rate of amputation from 25% to 50%<sup>23</sup>, as was the case in this series.

This study has several limitations. Anatomical lesions, joint revascularization procedures (open and endovascular), time to revascularization, levels of glycosylated hemoglobin and other markers, results of vascular laboratory tests, and survival and cost analyses were not investigated in this data set. The generalizability of our results is limited to the assessment of our patient population at a specific period in time. Moreover, in addition to endovascular revascularization, other strategies that might decrease the rate of amputation secondary to DM need to be further studied.

## Conclusions

The incidence of DF is increasing overtime. Revascularization by an endovascular approach may be a feasible alternative to reduce major amputation rates even in countries with high incidence of diabetes. However, further studies are required to support these conclusions.

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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 were performed on humans or animals for this study.

**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 the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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