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EVALUATION OF CLINICAL ASPECTS RELATED TO LOWER LIMB AMPUTATION AMONG INDIVIDUALS LIVING WITH TYPE 2 DIABETES MELLITUS IN MEXICO

EVALUACIÓN DE ASPECTOS CLÍNICOS RELACIONADOS CON LA AMPUTACIÓN DE MIEMBROS INFERIORES EN PERSONAS QUE VIVEN CON DIABETES MELLITUS TIPO 2 EN MÉXICO

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ABSTRACT

Introduction: Diabetes continues to be a leading cause of disability and death in the world's population. About 25% of people with diabetes will develop an ulcer in one of their lower pelvic limbs. **Objective:** The present study evaluates the clinical aspects related to lower pelvic limb amputation in a cohort of patients with diabetes mellitus. **Methods:** Retrospective, cross-sectional study, conducted in collaboration between the Mexican Institute of Social Security and the School of Pharmacy of the Autonomous University of Morelos State, involved a review of records of patients with type 2 diabetes mellitus at the Regional General Hospital "Ignacio García Téllez". One hundred clinical and electronic records were selected based on inclusion criteria, which included age over 18 years, affiliation at the study site, diabetes evolution of at least 10 years, pharmacological treatment for diabetes and diagnosis of diabetic foot with complete healing or amputation as an outcome. Statistical analyses were performed using STATA and ethical approval was obtained. **Results:** Patients with optimal glycemic control by quantifying their fasting glucose levels (<130 mg/dl) as well as their glycated hemoglobin values (< 7%) had a lower frequency of amputations (p<0.001; Chi2) compared to those patients without adequate glycemic control. **Conclusions:** Being male, glycosylated hemoglobin values greater than 7% and mean fasting glucose values greater than 130 mg/L were found to increase the likelihood of having a lower extremity amputation.

Keywords: Diabetes; Glycemic; Glycated hemoglobin; Pharmacotherapy; Major Amputation; Minor amputation. (Source: MESH-NLM)

RESUMEN

Introducción: La diabetes continúa siendo una de las principales causas de discapacidad y muerte en la población mundial. Alrededor del 25% de las personas con diabetes desarrollarán una úlcera en alguno de sus miembros pélvicos inferiores. **Objetivo:** El presente estudio evalúa los aspectos clínicos relacionados con la amputación del miembro inferior pélvico en una cohorte de pacientes con diabetes mellitus. **Métodos:** Estudio retrospectivo, transversal, realizado en colaboración entre el Instituto Mexicano del Seguro Social y la Facultad de Farmacia de la Universidad Autónoma del Estado de Morelos, implicó una revisión de expedientes de pacientes con diabetes mellitus tipo 2 en el Hospital General Regional "Ignacio García Téllez". Se seleccionaron 100 expedientes clínicos y Electrónicos basados en criterios de inclusión, que incluían edad mayor de 18 años, afiliación en el sitio del estudio, evolución de la diabetes de al menos 10 años, tratamiento farmacológico para la diabetes y diagnóstico de pie diabético con curación completa o amputación como resultado. Los análisis estadísticos se realizaron mediante STATA y se obtuvo aprobación ética. **Resultados:** Los pacientes con un control glucémico óptimo cuantificando sus niveles de glucosa en ayunas (<130 mg/dl) así como sus valores de hemoglobina glicosilada (< 7%) tuvieron una menor frecuencia de amputaciones (p<0,001; Chi2) en comparación con aquellos pacientes sin un control glucémico adecuado. **Conclusiones:** Se encontró que ser hombre, valores de hemoglobina glucosilada superiores al 7% y valores promedio de glucosa en ayunas superiores a 130 mg/L aumentan la probabilidad de presentar una amputación de extremidad inferior.

Palabras claves: Diabetes; glucémico; Hemoglobina glicada; Farmacoterapia; Amputación Mayor; Amputación menor. (Fuente: DeCS- BIREME)

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INTRODUCTION

Diabetes is a major global public health concern due to its high incidence and mortality rates. In Latin America, approximately 422 million people are affected by this disease [1,2] . This represents a significant challenge for healthcare systems worldwide and individuals grappling with this degenerative disease [3]. The International Diabetes Federation (IDF) reported that in 2021, 6.7 million people worldwide succumbed to diabetes-related complications, representing 12.2% of total global deaths [4]. Among the health complications of diabetes, ulcerative lesions in the lower pelvic limbs are one of the most observed. The risk of amputation in people living with diabetes is 15 to 40-fold higher compared to people without diabetes[5].

The ulcerative lesions manifest itself in up to 25% of patients living with diabetes [6] , with recurrence rates of 65% at 3-5 years, leading to major and minor amputations in 20% of the cases [7]. In Mexico, medical information on the prevalence and incidence of diabetic foot, amputations and the clinical aspects related to this surgical treatment is limited. However, the Mexican Institute of Social Security (IMSS) reported in 2004 an amputation rate of 169 per-100,000 patients living with diabetes, in 2013 the rate was 163 per-100,000 patients. They presented an average age of 61.7 years for major amputations and 65.4 years for minor amputations [8]. Another clinical cause of amputations is the manifestation of peripheral arterial disease. This is accelerated by direct damage to nerves and blood vessels resulting from high blood glucose levels [9,10].

In addition, the wound healing process is altered due to cellular factors involving vascular, immunological, neurological, inflammatory, and oxidative stress; alterations that lead to partial or total necrosis of the lower extremities by the induction of severe infections [11,12]. Lower pelvic limb amputations occur below or above the ankle joint. People with major amputations report greater pain, decreased social function, and less independence than those with minor amputations[13]. It is of utmost importance to consider that amputations significantly decrease the quality of life of people with diabetes[14]. Therefore, it is important to consider amputation as a mortality factor following surgery[15,16]. Consequently, there is a growing interest in developing strategies focused on diabetes prevention within healthcare systems. Recently, the Pan American Health Organization (PAHO) highlighted the importance of implementing prevention, monitoring, and control strategies for diabetes, particularly during the recent COVID-19 health emergency [3]. The present study evaluates the clinical aspects related to lower pelvic limb amputation in a cohort of patients with type 2 diabetes mellitus.

METHODS

Study design

In a collaborative effort between the Mexican Institute of Social Security (IMSS) and the Faculty of Pharmacy at the Autonomous University of Morelos state, a retrospective cross-sectional study was carried out, consisting of a detailed review of clinical records from patients living with type 2 diabetes mellitus assigned to the Regional General Hospital "Ignacio García Téllez" in the Morelos Delegation.

Population and sample

The clinical records of all patients living with type 2 diabetes mellitus were analyzed by reviewing the census of patients with diabetes in the family medicine information system. Two clinical pharmacist professionals were trained by two family medicine physicians to collect the information. Subsequently, the two medical professionals conducted a thorough review of the gathered data to validate compliance with the inclusion criteria. According to the International Classification of Diseases, a total of 2021 patients with multiple complications of diabetes, including vascular and neurological complications were identified, being included a total of 100 clinical records (CR) and Electronic Clinical Records (ECR) from patients who met the following inclusion criteria: age over 18 years, have a

valid affiliation at the study site, have verifiable diagnosis of Type 2 Diabetes Mellitus with documented history of diabetes for at least 10 years, receiving pharmacological treatment for diabetes, receiving medical attention in the setting of the study in the period January-May 2022, and having a verifiable diagnosis of diabetic foot with complete healing or surgical amputation as outcome. The exclusion criteria included CR of patients who had passed away before the outcomes were determined, records with fewer than 2 annual fasting blood glucose measurements, and CR from patients who had requested a transfer to a different healthcare facility.

Data processing

Once the CR and ECR were identified, we proceeded to perform further review using the family medicine service's archives, the ECR from the hospitalization service, and the clinical records from the emergency service of the Hospital. It was collected the clinical information related to foot lesions including type of lesion presented, grade according to Wagner and Meggit [17] classification, location of the lesion and presence of Charcot arthropathy. Information regarding the type of amputation, such as major or minor amputation of the lower pelvic limb, was also collected, as well as the history of pharmacotherapy used in the treatment of diabetes and diabetic foot. Other data such as age, sex, main comorbidities, and laboratory values (average glycated hemoglobin and fasting glucose levels within 6 months after the diabetic foot diagnosis) were also obtained.

Statistical analysis

The qualitative variables are presented as frequencies and percentages. For quantitative variables, the mean and standard deviation are presented. Bivariate mean comparison analyses were performed using the chi2 test and t-test. The results considered statistically significant were identified with $p<0.05$. Data were collected in a database using the Microsoft Excel program. All statistical analyses were performed using STATA version 12 (Statistical software).

Ethical Considerations

The present study was approved by the Local Research Committee and the Local Ethics Committee of the Mexican Institute of Social Security, Morelos (IMSS; number: R-2021-1701-040). All data from clinical records was processed using a codification and safeguarded by the researchers. No informed consent was required since this study only used clinical records.

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RESULTS

The study analyzed a total sample of 100 clinical records. Among the sample, 67% of the patients had comorbidities related to overweight and obesity, followed by systemic arterial hypertension (32%). (Table 1).

Table 1. General Information and comorbidities of patients diagnosed with diabetic foot.

Sex	
Female	**Male**
26(26%)	74(74%)
Mean age: 59.2 ±10.5 years	
Years of progression of Dm2	18.65 ±9.24 years
Co-morbidities	**Percentage n= 100**
BMI> 25 kg/m2	67
Obesity	33
SAH	32
CKD	15
Dyslipidemia	7

Diabetic Neuropathy	5
Diabetic Retinopathy	4

Dm2: Type 2 Diabetes; BMI: Body mass Index;
SAH: systemic arterial hypertension; CKD: Chronic Kidney disease.

It was also found that 74% of the patients with diabetic foot were male patients, while 26% were female. The average age of the population analyzed was 59 years, with an age range from 32 to 86 years. The 49% of the patients presented a total or partial amputation of the lower pelvic limbs. It was identified that 30% of the cases were submitted to a minor amputation surgical intervention while 19% underwent major amputation surgery. The right lower limb was predominantly more affected in the case of minor amputations, and 69.23% of the patients with major amputations had both lower limbs affected by diabetic foot (Table 2).

Table 2. Type of amputation and pelvic limb affected in the studied population.

Amputation	Affected limb (frequency/percentage) Right	Left	Both	Total
Major Amputation	5 (23.81)	5 (33.33)	9 (69.23)	19 (38.78)
Minor amputation	16 (76.19)	10 (66.66)	5 (38.46)	30 (61.22)
Total	21 (100)	15 (100)	13 (100)	49 (100)

The grade of the lesions was reported according to the Wagner-Meggit scale by the treating physicians We identified that 40% of the patients with diabetic foot presented grade IV lesions where there was already the presence of limited gangrene, followed by grade I lesions (28%), (Table 3).

Table 3. Diabetic foot lesions according to the Wagner and Meggit classification in the studied population.

Wagner Grade	Frequency (Percentage)	Sex Male	Female
I	28 (28)	15 (15)	13 (13)
II	11 (11)	9 (9)	2 (2)
III	6 (6)	5 (5)	1 (1)
IV	40 (40)	31 (31)	9 (9)
V	15 (15)	14 (14)	1 (1)
Total	100 (100)	74 (74)	26 (26)

Regarding the pharmacological management of diabetes, most patients (19%) received an insulin monotherapy regimen, followed by a combination of glyburide and metformin regimen. Meanwhile, 12% of the patients were prescribed a regimen of insulin in combination with metformin. (Figure 1).

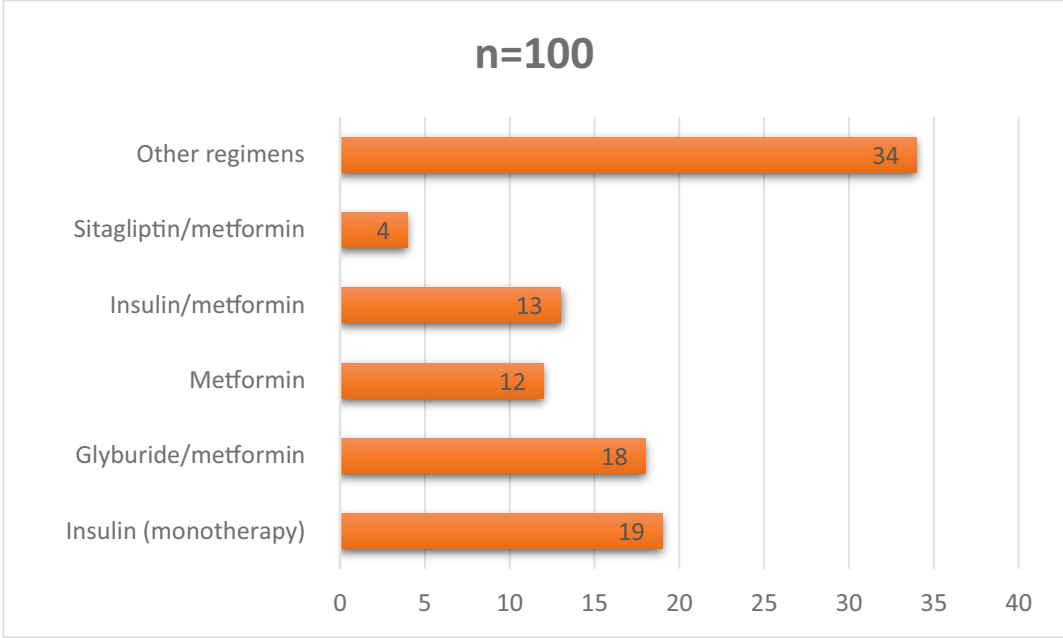

Figure 1. Main regimens of pharmacotherapy used in the treatment of diabetes in the patients included in the study.

It was performed a bivariate analysis showing that most of the patients with amputations were male, with statistically significant differences (p=0.031). Likewise, significance was identified in those patients older than 60 years of age in comparison with cases below that age (p=0.017). Amputations were also more frequent in patients with more than 10 years of diabetes evolution (p= 0.001) (Table 4). The degree of average glycemic control in the six months following the diagnosis of diabetic foot was an important variable in this study. In patients with optimal glycemic control by quantifying their fasting glucose levels (less than 130 mg/dl) as well as their glycated hemoglobin values (less than 7%) according to the criteria of the Mexican Official Standard 015 for the prevention, treatment, and control of diabetes [18], amputations were less frequent compared to those patients without adequate glycemic control. These biochemical parameters were statistically significant (p<0.001 and p=0.001, respectively) by Chi^2 test. Meanwhile, pharmacological treatments showed no relation with amputations.

When evaluating the possible relationship between comorbidities, smoking, systemic arterial hypertension, obesity and being overweight (BMI> 25kg/m2), as well as Charcot arthropathy and chronic kidney disease, no statistically significant differences were found between patients with amputations and those who did not undergo such surgical procedures (Table 4).

Table 4. Bivariate analysis of amputations recorded in the study population (* Chi^2).

Variable (n=100)	Without amputation n (%)	With amputation n (%)	p*
Male sex	8 (8)	41 (41)	0.031
Over 60 years old	32 (32)	19 (19)	0.017
Over 10 years of diabetes evolution	10 (10)	39 (39)	<0.001
Controlled fasting glycemia (<130 mg/dl) [18]	19 (19)	0(0)	<0.001

Controlled glycated hemoglobin (Hb1Ac < 7%[18])	23 (23)	7 (7)	0.001
History of Smoking	13 (13)	14 (14)	0.729
Glyburide use	10 (10)	15 (15)	0.204
Insulin use	25 (25)	25 (25)	0.841
Metformin use	34 (33)	33 (33)	0.942
SAH	32 (32)	24 (24)	0.118
BMI> 25 kg/m2	32 (32)	36 (36)	0.363
CKD	7 (7)	7 (7)	0.581

BMI: Body mass Index; SAH: Systemic Arterial Hypertension; CKD: Chronic Kidney disease.

DISCUSSION

In our study population we found that male patients had a higher frequency of diabetic foot (74%), as has been reported internationally [19]. In particular, the percentage obtained in our study was similar to that observed by Sharma[21] in 2016 in India (78.64%) and the reported by Vanherwegen [20] in Belgium (72%). This could be explained by considering that, as reported in the study conducted by Rangel [22] on a Mexican population sample in 2017, women tend to exhibit greater adherence to lifestyle changes and medication regimens which is associated with a lower risk of developing foot lesions.

The mean age of patients with diabetic foot obtained in this study (59.2± 10.5 years) was very similar to that also reported by Sharma [21] (55.09±10.30 years), and contrasts with the reported by Vanherwegen [20] (69.7±0.3 years). This is mainly explained by the demographic differences in the countries in which the studies were carried out. We found an average time of evolution of diabetes of 18.65 (±9.24) years at the time of diagnosis of diabetic foot. This contrasts with that obtained by Nuñez [23] in Honduras in 2017, who observed an average of 10±8.0 years of time of evolution.

The average age of patients with major amputation was 55.3±11.2 years, while for minor amputations, it was 59.24±11.2 years (data not shown in the tables). This is particularly relevant because the mean age for major amputations reported in 2013 by Cisneros [18] for the Mexican population was 61,7 years. This indicates that diabetic foot outcomes are occurring at earlier age in our study population.

Age and time of evolution of diabetes, may be related to the slow progression of vascular and neuropathic damage caused by diabetic foot ulcers, as is reported by Zhang [19], who reports a longer diabetes evolution in patients with diabetic foot ulceration compared with those without a diabetic foot ulcer (11.3 ± 2.5 versus 7.4 ± 2.2 years). Our results, and those reported by Sharma and Nuñez, correspond to populations from developing countries, in which certain factors such as limited access to healthcare services, insufficient prevention programs, and medical service overload may promote the onset of diabetic foot, for instance, the limited access to clinical services.

Such conditions require further exploration. The main comorbidities found in this research were overweight and obesity (BMI> 25 kg/m2) in 67% of the patients, followed by systemic arterial hypertension (32%), in contrast, Nuñez[23] observed peripheral vascular disease (72%) and systemic arterial hypertension (69.6%) as the main findings. It should be noted that the Mexican population exhibits one of the highest prevalence

rates of overweight and obesity on a global scale. Recently, Barquera [24] reported an increase in the incidence of obesity of 42% between 2000 and 2018 in Mexican population.

It is also known that such metabolic conditions are related to cardiovascular diseases like systemic hypertension, which is highly spread also in the Mexican territory (prevalence of 9.6% according to ENSANUT 2021[25]). Our study also showed that 49% of patients diagnosed with diabetic foot underwent major or minor amputation of the lower pelvic limb. This result differs from the 30.43% documented by Bekele [26] in Ethiopia in 2020. This difference may be explained by multiple sociodemographic and cultural differences, genetic variability between populations, and variations in the provision of health care in these territories.

It is important to highlight that the 49% we observed is a remarkably high rate, undoubtedly this result suggest the limited access that certain populations have to a proper clinical follow up. It is however clear that we can expect that the population we studied was exposed to several factors that led to this outcome, the amputation of a lower pelvic limb, some of which are linked to limited pharmacotherapy access and medical assistance; non-adherence to therapy, or the lack of proper primary care policies for such vulnerable populations like the people living with diabetes. It has also been reported the barriers that may affect the proper foot care, are access to information and timely clinical appointments from health care providers[27].

In relation to the grade of the lesions described in this study, the results align with those identified by Ugwu[28] in Nigeria in 2019, where the most common lesions were grade IV according to the Wagner scale. This grade of damage implies the presence of gangrene, which increases the risk of amputation. In contrast, our findings differ from those obtained by Bekele[26], who identified that 72% of cases presented lesions ranging from grade I to III, a percentage that in our study was 45%. This observation could potentially be attributed to the possibility of an early detection and therapeutic intervention in the case of these lesions, mitigating their progression towards the more severe grade IV or V categories. Regarding pharmacotherapy, most patients with diabetic foot were treated with insulin (19%). However, Navarro [29] in 2016 identified that the development of diabetic foot is not directly related to insulin. It is well known that adherence to insulin is usually lower compared to orally administered medications, and it is likely to worsen due to other factors such as lack of social support and especially the difficulty in measuring adequate insulin units, among others[22,30].

The present study found that amputations were less frequent in patients over 60 years. Possibly, due to the establishment of better conditions provided by a care giver or the provision of a therapeutic scheme that allowed long-term improvement of glycemic control; such conditions need to be further studied. Having an adequate fasting glucose level (<130 mg/dl), glycated hemoglobin levels below 7%, and being female were variables related to non-amputations.

This finding is similar to the research conducted by Vatankhah[31] in 2016, who identified that amputations were 8.7% more frequent in those patients with higher glycated hemoglobin values. This result is also in accordance with that reported by Fan [32] in 2021, who reports a higher risk of amputation in males (OR:1.38, p<0.001). This study remarks the high prevalence of diabetic foot in patients with type 2 diabetes mellitus in Mexico.

While results were compared with those from other countries, it is essential to consider the differences in healthcare systems, medical practices, and sociocultural factors that may influence the prevalence, management, and outcomes of the diabetic foot. These contextual disparities are crucial for gaining a better understanding of the situation in Mexico and provide significant insights into this specific population. It is noteworthy that, internationally, amputation rates have been reported to vary from as low as 3% in China to as high as 42.8% in Taiwan[33], placing our study

population among the higher rates of amputation. Therefore, it is recommended that future research delves more deeply into the impact of medical practices and factors related to the healthcare received by these individuals, as well as the effect of prevention policies and programs on the risk of amputation in diabetes patients. Previous evidence has demonstrated the effectiveness of these strategies in other settings[34,35].

The main limitations of this study are related to the quality of the information contained in the clinical records which could have introduced biases in patient selection due to the possibility of underreporting in the diagnosis of diabetic foot. It is common for physicians to record only the presence of complications in the census, without specifying more precisely that it is diabetic foot. Additionally, deficiencies were identified in the completion of medical notes in the clinical records, as in most cases, there was a lack of detailed information on clinical characteristics and the extent of the lesions, as well as more comprehensive information on the onset of the lesions and potential risk factors identified in the physical examination. Having this data could have significantly expanded the scope of this research.

CONCLUSIONS

After the analysis performed in the study population, it was found that being male, having glycated hemoglobin values higher than 7% and having average fasting glucose values higher than 130 mg/L increase the probability of presenting a lower extremity amputation while other factors such as being older than 60 years and having and an optimal periodic measurement of glucose and glycated hemoglobin seem to be factors related to a lower risk.

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Authorship contribution: PAJC, TJC and MNA participated in the conception and design of the article, analysis and interpretation of the data. PAJC and TJC participated in the reaction to the article. GGDL, AED and AJL participated in the critical review of the article, approval of the final version. Finally, AED and AJL provided technical and administrative advice at the study headquarters.

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