



RISK FACTORS FOR AMPUTATIONS IN PEOPLE WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Introduction: The objective is to determine the main risk factors for the development of amputations in people with DM2. **Material and Methods:** A case-control study was carried out with 134 cases (people with DM2, with amputation in the pelvic limb) and 134 controls (people with DM2, without amputation in the pelvic limb). The association of variables was analyzed by Odds Ratio and a multivariate analysis model with logistic regression. **Results:** The final logistic regression model with the independent variables of years of DM2, history of ulcers, PAD, increases in HbA1c and ND. The value of R² of Nagelkerke indicates that the proposed model explains 65% of the variance of the dependent variable. The percentage of success of the affirmations in function of the prediction indicates that there is an 82% probability of success in the result of the dependent variable, when I know the independent variables of the model. **Conclusions:** The main risk factors for the development of amputations in people with DM2 are: the history of ulcers, PAD, ND and HbA1c, in that order of importance according to their degree of association with the appearance of amputations.

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INTRODUCTION

The transcendence of the study relies on identifying the main reasons of why amputations need to be realized, and to prevent them; where the 46% of people with Diabetes Mellitus type 2 (DM2) do not realize any preventive measure to avoid the complications, according to the report by the *Encuesta nacional de salud y nutrición 2016* (ENSANUT 2016), where

only the 9% of people were proportioned with health education^[1], the main causes for the development of amputations in people with DM2 will be studied, identifying the proper handling of physical explorations to the people that assist to the health services, and what kind of preventive measures are made to avoid the development of the diabetic foot, which makes the 85% of amputations^[2].

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DM2 is considered as the main cause of non-traumatic amputation on inferior limbs [3]. Where after presenting an upper amputation, (supracondylar) the survival rate in 3 years is of 50% and in 5 years only 40% of people will survive [4].

The DM2 is an epidemic in Mexico that, according to data of the *Instituto de estadística y geografía* (INEGI), 98 thousand deaths by diabetes were registered during 2015 [5]. In Jalisco it occupies the first place on deceases with a mortality rate of 71 for every 100,000 inhabitants [6].

According to the report of ENSANUT 2016 [1] the prevalence of DM2 in Mexico is of 9.4%, where respecting to the complications, it was reported that the ulcers represented the 9.1% of cases (in 2012 only the 7.2) and the amputations the 5.5%, more than double of the reports in 2012 (2%) [1]. Of the implemented preventive measures by people on the last year, 21% of them did revise their feet [1].

In the study realized by Chu [7] in 2016 it was determined that the glycosylated hemoglobin (HbA1c) >9% represent a Hazard Ratio (HR) of 1.12 for the fingers amputation and a HR of 1.08 for the re-ulceration [7].

Mohammedi [8] analyzed in 2016 the association of the peripheral arterial disease (PAD) with the amputations, determining that the risk of the PAF associated to chronic ulceration in inferior limbs presents a HZ of 1.59 (IC [1.15-2.22], $p=0.006$) [8].

The objective is to determine the main risk factors for the development of the amputation in people with diabetes mellitus type 2.

MATERIAL AND METHODS

Case-control studies were made matched with a reason of 1:1 counting with a total of 268 persons with DM2 diagnosis included in this paper, from which 134 were cases (of DM2 with amputation) and 134 were controls (of DM2 without amputation).

The cases were compared against the controls making a sex and age matching in a five year period, the inpatient controls being one per each case.

The study was made in Mexico, in a second level hospital, in the year 2017, a digital and physical revision of the expedients was made in the services of intern medicine, thorax and cardiovascular, endocrinology and orthopedic.

A stratified random probabilistic sample was made in function of the different stratus with simple allocation. The sample was made with the formula: $n = z^2 p q / d^2$, Donde $q = 1 - p = 0.945$, $p = 5.5\% = .055 =$ Prevalence of reported amputations in ENSANUT 2016, $z = 1.96 =$ 95% confidence interval, $d = 0.05 = 5\%$ standard error. Obtaining the sample size of: $n = 80$. The criteria of inclusion were: people with diabetes mellitus type 2 of 10 years of evolution or more, metabolic decontrol with ciphers of HbA1c of 7 to 16% (in case of not counting with HbA1c were included in the study to determine the lack of proof realization), with or without ulcers historical in the pelvic member, presenting ulcers with or without infections, including or not variables of hypertension, smoking, obesity, dyslipidemia, distal sensitive diabetic neuropathy, ischemic processes or peripheral arterial disease. For the cases with amputation of pelvic member and for the controls without amputation for the pelvic member.

The analysis of the relation between the risk factors with the amputation was made throughout the association mean Odds Ratio (OR) and a multivariate analysis with logistic regression, to precede the probability in which the amputations appears according to the independent variables as risk factors; the main independent variables were the following: evolution years, ulcers historical, PAD, diabetic neuropathy (DN), the rise in the HbA1c and they were related with the dependent variable of amputation. For the data analysis the IBM SPSS Statistics 21 was utilized.

A free and informed consent was obtained, by part of the participants, with basis in the article 6 of the Universal Declaration of Human Rights and the articles 21, 22 and 23 of the *Reglamento de la ley general de salud en materia de investigación para la salud*.

The research was approved by the *Comité de investigación y ética* of the second level hospital. A state register was asked by part of the *Secretaria de salud Jalisco*, giving the state register number 0165/17 HCJIM/2017.

RESULTS

268 persons were studied (134 cases and 134 controls). The presented sociodemographic characteristics in this research, age and genre between cases and controls there is no statistic difference, the groups were homogenous. The scholar groups that presented the highest prevalence for the development of amputations were the ones who did not completed elementary school with 25% and the ones with elementary school with 40%, presenting a higher number of amputations in comparison to the groups of junior high with 15%, high school with 7% and university with only the 2%. Establishing an inverse correlation, the lower the scholar preparation the higher number of amputations.

Respecting the comparison of the cases and controls with the risk factors of elevated glucose in fasting with more than 130 mg/dl, elevated triglycerides with more than 150 mg/dl, HDL low cholesterol catalogued with lows of 40 mg/dl and LDL high cholesterol catalogues as higher to 100 mg/dl, a positive association was found with an OR of 1.1 and a $p=0.9$ for the glucose, the triglycerides with an OR of 1.3 and a $p=0.5$, the HDL cholesterol with an OR of 11.2 and a $p=0.01$, the LDL cholesterol with an OR of 1 and a $p=0.9$. Look table 1.

Table 1 Glucose association and the lipids profile as risk factors for the presence of amputations.

| Variables | Cases | | Controls | | OR | IC 95% | P value | |
|----------------|------------------|----|----------|----|------|--------|----------|------|
| | n | % | n | % | | | | |
| Glucose | 131 – 1117 mg/dl | 89 | 77 | 81 | 76 | 1.1 | 0.6-2 | 0.9 |
| | 80 – 130 mg/dl | 26 | 23 | 25 | 24 | | | |
| Triglycerides | 151 – 1165 mg/dl | 26 | 48 | 24 | 42 | 1.3 | 0.6-2.7 | 0.5 |
| | < 150 mg/dl | 28 | 52 | 33 | 58 | | | |
| Colesterol HDL | < 40 mg/dl | 47 | 97.9 | 42 | 80.8 | 11.2 | 1.4-91.1 | 0.01 |
| | 41 – 66.4 mg/dl | 1 | 2.1 | 10 | 19.2 | | | |
| Colesterol LDL | 101 – 304 mg/dl | 12 | 24 | 13 | 25 | 1 | 0.4-2.3 | 0.9 |
| | < 100 mg/dl | 38 | 76 | 39 | 75 | | | |

Source: direct.

These ones were determined for the study for the main risk factors for the amputations presented in table 2.

Table 2 Association of the main risk factors with the presence of amputations.

| Variables | | Cases | | Controls | | OR | IC 95% | Value of p squared chi of Mantel-Haenszel |
|----------------------|-------------|--------------------|----|----------|----|---------|----------|-------------------------------------------|
| | | n | % | n | % | | | |
| Ulcers historical | Si | 132 | 98 | 44 | 33 | 135 | 31.9-571 | 0.00 |
| | No | 2 | 2 | 90 | 67 | | | |
| Exact test of Fisher | | IC 95%= 33.2-153.7 | | | | p= 0.00 | | |
| PAD | Si | 55 | 41 | 9 | 7 | 9.6 | 4.5-20.5 | 0.00 |
| | No | 79 | 59 | 124 | 93 | | | |
| ND | Si | 48 | 36 | 10 | 8 | 6.9 | 3.3-14.4 | 0.00 |
| | No | 86 | 64 | 124 | 92 | | | |
| | >8% | 71 | 53 | 55 | 41 | | | |
| HbA1c | 7 a 7.9% | 16 | 12 | 32 | 24 | 2.6 | 1.3-5.2 | 0.01 |

Source: direct

A multivariate analysis with a logistic regression model with all the independent variables to determine its association with the dependent variable (amputation), backwards elimination strategy was selected, resulting in 5 significant variables. Based on these results it was decided to conform the final model of multivariate logistic regression to the independent variables of the evolution years of the DM2, ulcers historical, PAD, augmentation of HbA1c and diabetic neuropathy.

The punctuation of statistical efficacy of ROA indicates that there is a significant improvement in the prediction of the occurrence probability of the dependent variable categories ($p < .001$).

The value of R^2 of Nagelkerke indicates that the proposed model explains the 65% of the variance of the dependent variable (.650). With a significance of 0.187 according to the goodness-of-fit test from Hosmer and Lemeshow of data adjustment of the regressive logistic model.

The successful percentage of affirmations in function of the prediction indicates that there is an 82% of successful probability in the result of the dependent variable, when the evolution of the DM is well known, the ulcers historical, the PAD, the augmentation in the HbA1c and the diabetic neuropathy.

Wald's punctuation for the proved model indicates that the independent variables of the ulcers historical, PAD, and diabetic neuropathy give significantly to the prediction of the dependent variable, the obtained results can be generalized towards the population (Wald 17.5 [$p < .001$], 9 [$p = .003$], 9.5 [$p = .002$]). See table 3.

Table 3 Final logistic regression model for the association of amputations with the most significant independent variables.

| Variable | Wald | Value of p | Affirmation percentage | Squared R of Nagelkerke | Test of goodness of Hosmer and Lemeshow |
|-----------------------|--------|------------|------------------------|-------------------------|-----------------------------------------|
| Years of DM2 | .014 | .907 | | | |
| Ulcers | 17.529 | .000 | | | |
| PAD | 9.014 | .003 | 82.2 | 0.65 | 0.187 |
| Augmentation of HbA1c | .035 | .851 | | | |
| Neuropathy | 9.475 | .002 | | | |

Source: direct.

DISCUSSION

The main identified prognostic factors for the development of amputations in people with DM2 are: ulcers historical, PAD, diabetic neuropathy and the augmentation in the HbA1c, in that importance order according to its association degree with the appearance of amputations. These factors were determined by a statistical analysis with the association mean of OR and a multivariate analysis with logistic regression. The significance of these results for people who suffer of DM2 are quite important for the prevention of the complications of the disease, because it can be translated in positive results to improve the quality of life of these people, to avoid that they develop these complications.

Respecting to the multivariate analysis with logistic regression, it highlights its transcendence in the study to predict the probability that an amputation appears, respecting to the independent variables as risk factors.

The final logistic regression model by mean of R^2 of Nagelkerke indicates that the proposed model explains the 65% of the variance in the dependent variable (amputation). Which helps to predict a high percentage in the occurrence of the event of interest. The result can be compared with the study realized by López and Yanes (2016) [9] where throughout of a multivariate analysis with logistic regression, they found that the variables of age, time, ischemic cardiopathy and hyperlipidemia showed a statistical significance association was shown, obtaining a R^2 of Nagelkerke of 0.15, this logistic regression model explains the 15% of the variance of the dependent variable (diabetic foot).

The multivariate analysis with logistic regression done in the paper is the sum of the transcendence given that a R^2 of Nagelkerke of 0.65 was obtained, corresponding to the association of the evolution years of the DM2, ulcers historical, PAD, augmentation of HbA1c and diabetic neuropathy, in comparison with the R^2 of Nagelkerke of only 0.15 obtained by López and Yanes [9], this logistic regression only explains the probability to develop a diabetic foot in the 15% of cases, with our study it was demonstrated that up to the 65% of cases of amputations in people with DM2 can be diagnosed, it is very important the prevention to avoid a higher incidence of amputations in people with DM2.

It was determined that people with ulcers historical have 135 more risk of presenting an amputation than people without it. The limitation of the study is that it does not have the criteria for a correct statistical analysis in the squared chi of Mantel-

Haenszel because they do not presented in each box of the 2x2 table in the observations number of at least 5 each, it was decided to realize the Fisher's exact proof obtaining an IC 95%=33.2-153.7 and a $p=0.00$ for the statistical significance, the ulcers presence association with amputations is significant being that the 75% of people that presented ulcers historical suffered an amputation, presenting a parallelism with other studies [2] where it was identified that the amputations were precedes in a 85% by ulcers, whereas people who did not presented ulcers was of only 2%. It is fundamental the ulcers prevention to avoid any amputations.

People with DAP have 9.6 more risk of presenting an amputation than people without it. This is similar to that found by other authors in people with DM2, like in India Mohammedi *et al.* [8], where they found a positive association of the presence of DAP associated to a high risk of presenting an amputation with a Hazard ratio of 1.59.

The DAP is a strong diagnose marker for the development of amputations, where in this study it was identifies that those patients that presented DAP in 86% they presented an amputation as well.

It was identified that a high augmentation of the HbA1c presents a higher risk of presenting an amputation, founding a positive association between patients that presented an HbA1c higher to 8% with the higher number of amputations. People that present an HbA1c higher than 8% have 2.6 more risk of presenting an amputation that people with ciphers lesser than 8%.

It was decided to establish the HbA1c higher to 8% as a risk factor, because of the previous results in other studies as the one of Chu *et al.* [7] where it was determined that the HbA1c >9% represents a HR of 1.12 for the amputation of foot fingers and a HR of 1.08 for re-ulceration, it was decided to establish with lower ciphers of HbA1c that the ones presented, even though they were pathological an association towards amputations was still being presented.

Observing that asides of the augmentation of the HbA1c higher to 8% is still a predictive marker for the development of amputations, because of this, the importance of keep doing this study to prevent any complications of DM, of the 268 included patients 94 did not have this test, 35%.

The ulcers historical, DAP, diabetic neuropathy and the augmentation in the HbA1c were identified as the main risk factors.

CONCLUSION

For the prevention of amputations and main pathologies that take to their development, it is fundamental the metabolic control throughout an adequate control with the ciphers of HbA1c.

To improve the health attention for people with DM2 a continuous capacitation program is necessary for the health professionals that help them to improve their services towards people with DM2, giving a better attention with easy access clinical tools for the health workers with great importance on the prevention of the complications such as the measurement of the ankle arm index, monofilament test and the correct classification by lesions according to the classification of the university of Texas, to achieve a proper detection and identification of the feet in risk situation.

To achieve that people have more consideration towards their health, education programs must be implemented with the objective of people knowing the dangers and benefits that takes when they follow their treatment, throughout a correct diet and physical activities that have to follow to improve and conserve their health. Illustrative information will be useful as well to know the complications that DM has and the teaching of specific actions to do at home to avoid the presence of feet lesions.

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