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# Lower limb wounds in diabetic and nondiabetic patients: survival analysis

Feridas em membros inferiores em diabéticos e não diabéticos: estudo de sobrevida Heridas en miembros inferiores en diabéticos y no diabéticos: estudio de supervivencia

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#### **ABSTRACT**

**Objective:** To evaluate the survival of wounds in lower limbs of diabetic and non-diabetic patients.

**Method:** Retrospective cohort study of patients with lower limb ulcers treated at a specialized center between 2011 and 2013. Outcome: healing of lower limb injuries in days. The survival function of lower limb wounds and the differences between diabetic and non-diabetic were analyzed. The Log-rank test was used to compare the survival curves between the study groups.

**Results:** In up to 600 days, 23% of the diabetic patients presented wound healing, while 63% of the non-diabetic patients had their wounds healed, with a statistically significant difference in survival curves in comparison between the groups. The Hazard Ratios (RH) of healing were lower for diabetic patients (HR = 0.13, 95% CI = 0.02-0.97).

**Conclusion:** The results show that there is a delay in wound healing in diabetic patients. **Keywords:** Wound healing. Diabetes mellitus. Survival analysis. Incidence. Epidemiology.

# **RESUMO**

**Objetivo:** Avaliar a sobrevida de feridas em membros inferiores de pacientes diabéticos e não diabéticos.

**Método:** Estudo de coorte retrospectivo de pacientes com úlceras de membros inferiores tratados em centro especializado entre 2011 e 2013. Desfecho: cicatrização de lesões de membros inferiores em dias. Realizou-se análise da função de sobrevida das feridas de membros inferiores e das diferenças entre diabéticos e não diabéticos. Aplicou-se o teste Log-rank para comparação das curvas de sobrevida entre os grupos de estudo.

**Resultados:** Em até 600 dias, 23% dos diabéticos apresentaram cicatrização das feridas, enquanto 63% dos não diabéticos tiveram suas feridas cicatrizadas, com diferença estatística das curvas de sobrevida na comparação entre os grupos. Os Hazard Ratios (HR) de cicatrização foram menores para pacientes diabéticos (HR = 0,13, IC95% = 0,02-0,97). Conclusão: Os resultados mostram que há retardo na cicatrização de feridas em pacientes diabéticos.

Palavras-chave: Cicatrização. Diabetes mellitus. Análise de sobrevida. Incidência. Epidemiologia.

#### **RESUMEN**

**Objetivo:** Evaluar la supervivencia de las heridas en miembros inferiores de pacientes diabéticos y no diabéticos.

**Método:** Estudio de cohorte retrospectivo de pacientes con úlceras de miembros inferiores tratados en centro especializado entre 2011 y 2013.

**Conclusión:** cicatrización de lesiones de miembros inferiores, en días. Se realizó un análisis de la función de supervivencia de las heridas de miembros inferiores y de las diferencias entre diabéticos y no diabéticos. Se aplicó el test Log-rank para la comparación de las curvas de supervivencia entre los grupos de estudio.

**Resultados:** En un total de 600 días, el 23% de los diabéticos presentaron cicatrización de las heridas, mientras que el 63% de los no diabéticos tuvieron sus heridas cicatrizadas, con diferencia estadística de las curvas de sobrevida en la comparación entre los grupos. Los Hazard Ratios (HR) de cicatrización fueron menores para pacientes diabéticos (HR = 0,13, IC95% = 0,02-0,97). Conclusión: Los resultados muestran que hay retraso en la cicatrización de heridas en pacientes diabéticos.

Palabras clave: Cicatrización de heridas. Diabetes mellitus. Análisis de supervivencia. Incidencia. Epidemiología.

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# **■ INTRODUCTION**

Chronic Non-communicable Diseases (CNCD) currently account for 38 million cases of deaths per year worldwide, and of these cases, more than 14 million deaths occur between the ages of 30 and 70 years, of which 85% are in developing countries<sup>(1)</sup>. In Brazil, CNCDs have also a significant impact, especially circulatory system diseases (31%), neoplasias (17%), chronic respiratory diseases (6%) and Diabetes mellitus (6%)<sup>(1)</sup>.

Diabetes mellitus (DM) represents a major public health problem worldwide. About 382 million people have DM and 80% of them live in low and middle-income countries<sup>(2)</sup>. According to the International Diabetes Federation, in 2013 Brazil had the highest number of diabetics in South and Central America, corresponding to 11.9 million people<sup>(3)</sup>. Information from the telephone-based surveillance of risk and protective factors for non-communicable chronic diseases (Vigitel) reveal a significant increase in self-reported cases of DM in individuals over 18 years of age between 2006 and 2013<sup>(4)</sup>. In 2013, the prevalence of the disease was higher among individuals with lower educational level and its incidence has increased with population aging, affecting mainly individuals aged 45 and older<sup>(4)</sup>.

DM has systemic repercussions in the long term and its complications can be classified as acute and chronic<sup>(5)</sup>. Chronic complications include nephropathies, retinopathies, neuropathies and vasculopathies, and the latter two are the main complications responsible for the onset of wounds in the lower limbs (LLL) and feet<sup>(2, 6)</sup>.

Wounds caused by diabetic neuropathy can occur in various ways. However, the most common is the one due to sensory-motor and autonomic neuropathy, which causes muscle weakness and pathological anatomical and peripheral neurological disorders in the feet, as well as skin disorders (dryness and fissures), which may favor the onset of ulcers<sup>(6)</sup>. These wounds result from traumas often not perceived by patients due to decreased sensitivity or loss of sensitivity to pain<sup>(6)</sup>.

Regardless of their etiology, chronic wounds have high incidence rates, reduce patients' quality of life and cause massive socioeconomic impact on family members and health services<sup>(6-7)</sup>. Chronic venous ulcers are the most frequent and more than 70% of them do not heal even when appropriate topical therapy and compressive therapy are administered, leading to relapses<sup>(8)</sup>. Arterial wounds, for example, are the main cause of amputation.

In view of the aforementioned, the present study aimed to assess the survival of wounds in lower limbs of diabetic and non-diabetic patients.

#### **METHODS**

Article based on a monograph submitted to Universidade Federal de Minas Gerais (UFMG), in 2015<sup>(9)</sup>. Retrospective cohort study that used convenience sample (without sample size calculation), composed of 78 individuals treated at a specialized center for wound healing of a private hospital in the city of Belo Horizonte, Minas Gerais between January 2011 and December 2013.

The Wound Healing Center (CCF) is an outpatient clinic located in the Center-South region of Belo Horizonte specialized in the diagnosis and treatment of skin wounds. With a team composed of clinicians, orthopedists, vascular and plastic surgeons, nurses, nursing students, nursing technicians and a podiatrist, the service offers multidisciplinary care to the users. Patients with wounds caused by different etiologies such as venous insufficiency, arterial insufficiency, diabetic neuropathy, pressure ulcer and burns are treated in the referred service.

Patients with lower limb ulcers of vascular etiology, caused by arterial or venous insufficiency, and neuropathic ulcers were included and patients with pressure ulcers, burns and soft tissue lower limb trauma were excluded. Data was collected in January-February 2015 by two trained researchers and occurred in two stages: in the first, the medical records of the patients seen in the outpatient clinic were analyzed. In the second stage, in-person or telephone interviews were conducted with the patients, and these were asked to inform socio-demographic data not included in the medical records. Systematized data collection was done through a structured questionnaire with socio-demographic and clinical information, comorbidities, history of the disease and information about the treatment.

The outcome or dependent variable was the time to the healing of LLL lesions, in days. The independent variables were: sex, age, body mass index (BMI), schooling, diabetes mellitus, smoking, type of ulcer - arterial, venous or neuropathic, Unna boot, compressive therapy, bypass, angioplasty, surgical debridement, minor amputation (defined as amputation of toes or of the forefoot), major amputation (defined as forefoot proximal amputation), and skin grafting.

Descriptive analysis of categorical variables was presented by absolute and percentage frequencies, and of continuous variables, with the use of measures of central tendency. The healing rate in number of events/1000 persons/day was calculated.

In survival analysis, wound healing defined as the epithelialization of 90% or more of the affected area was considered an event. At the end of the study, patients lost

to follow-up, as well as those whose wounds did not heal until the last day of data collection or else died during the study period were censored and excluded, contributing to the latest time point available. Twenty-six patients were censored, and the dates of censorship were those included in the last note in the patients' records.

Survival of lower limb wounds was estimated using Kaplan-Meier technique (KM), and comparison of curves was performed using the Log-rank test. Also, unadjusted 95% confidence intervals (95% CI) were estimated using the Cox proportional hazards model, stratified by diabetics and non-diabetics. The assumption of proportionality required for the Cox model was tested with the graphical method. A significance level of 0.05 was adopted for all analytical procedures. A significance level of 0.05 was adopted for all analytical procedures.

Statistical analyzes were performed using Statistical Software for Professionals (Stata), version 14.0<sup>(10)</sup>.

The study was approved by the Research Ethics Committee of the hospital where the outpatient clinic is located (Protocol no. 799.991) and the participants signed the Informed Consent Form (TCLE) prior to the beginning of the treatment.

# **RESULTS**

Seventy-eight (78) patients were recruited. Of these, 48 (61.54%) were diabetic. The median value of healing time was 248 days (IQ = 125-492). Twenty-six cases of healing were recorded, with 27,271 days being the total follow-up time. Thus, the healing rate was 0.95 healing/1000 persons-days (95% CI = 0.65-1.40). The frequencies of the sociodemographic and health variables are presented in Tables 1 and 2.

There was a predominance of females: 45 (57.7%) women; 54 (69.2%) individuals were over 65 years: 52 (70.3%) individuals were overweight; 41 (62.1%) individuals had low educational level, and 49 (63.6%) were non-smokers. As for the variable age, it ranged from 36 to 93 years, with a median of 72 years (IQ = 61-79). The main surgical interventions undergone by the patients include angioplasty in 21 (26.9%) patients, surgical debridement in 14 patients (17.9%) and grafting in 13 (16.7%) patients. Regarding amputations, 12 patients (15.4%) of the sample underwent minor amputations and 3 patients (3.8%) underwent major amputations. It should be noted that, due to the different rates of nonresponse to the variables analyzed, the totals may vary.

**Table 1 –** Frequencies of sociodemographic variables, BMI and smoking in the total sample

Variables	San	Sample			
variables	n*	%			
Gender					
Male	33	42.3			
Female	45	57.7			
Age range (years)					
18-65	24	30.8			
>65	54	69.2			
ВМІ					
Not overweight	22	29.7			
Overweight	52	70.3			
Education					
Incomplete secondary education to complete higher education	25	37.9			
Illiterate to complete primary	41	62.1			
education	41	02.1			
Smoking					
Non-smoker	49	63.6			
Smoker	3	3.9			
Ex-smoker	25	32,5			

Source: Research data. Note: \*Number of individuals.

**Table 2 –** Frequencies of health variables in the total sample

	Sample			
Variables	n*	(%)		
Arterial ulcer				
Absence	48	61.5		
Presence	30	38.5		
Venous ulcer				
Absence	40	51.3		
Presence	38	48.7		
Neuropathic ulcer				
Absence	53	68		
Presence	25	32.1		
Unna boot				
Used	22	28.2		
Did not use	56	71.8		
Compressive therapy				
Used	51	65.4		
Did not use	27	34.6		
Bypass				
Did not undergo	73	93.6		
Underwent	5	6.41		
Angioplasty				
Did not undergo	57	73.1		
Underwent	21	26.9		
Surgical debridement				
Did not undergo	64	82.1		
Underwent	14	17.9		
Minor amputation				
Did not undergo	66	84.6		
Underwent	12	15.4		
Major amputation				
Did not undergo	75	96.2		
Underwent	3	3.8		
Skin grafting				
Did not undergo	65	83.3		
Underwent	13	16.7		
Source: Research data				

Source: Research data. Note: \*Number of individuals

Table 3 shows the healing rates according to sociodemographic and health variables, stratified by the presence or absence of diabetes.

**Table 3 -** Incidence rates of healing (events/1000 persons-day), according to sociodemographic and health variables, stratified by diabetic and non-diabetic patients

Variables	Total sample	Diabetics	Non diabetics	
Gender				
Male	0.74	0.57	1.12	
Female	1.2	0.81	1.8	
Age range (years)				
18-65	0.92	0.76	1.17	
>65	0.97	0.62	1.74	
вмі				
Not overweight	0.85	0.6	1.28	
Overweight	0.92	0.66	1.44	
Education				
Incomplete secondary education to complete higher education	0.85	0.79	1.09	
Illiterate to complete primary education	0.94	0.64	1.37	
Smoking				
Non-smoker	1.13	0.86	1.76	
Smoker	1.13	1,61	0.87	
Ex-smoker	0.67	0.3	1.33	
Arterial ulcer				
Absence	1.11	0.84	1.4	
Presence	0.72	0.52	1.9	
Venous ulcer				
Absence	0.61	0.55	10.99	
Presence	1.35	1.24	1.39	
Neuropathic ulcer				
Absence	1.11	0. 1	1.48	
Presence	0,63	0,64	-	
Unna Boot				
Did not use	0.83	0.67	2.62	
Used	1.17	0.68	1.26	
Compressive therapy				
Used	0.72	0.64	1.34	
Did not use	1.53	1.62	1.53	
Bypass				
Did not undergo	0.99	0.7	1.54	
Underwent	0.64	0.47	0.98	
Angioplasty				
Did not undergo	1.16	0.92	1.53	

Underwent	0.4	0.17	0.98
Surgical Debridement			
Did not undergo	1.08	0.85	1.47
Underwent	0.49	0.21	1.58
Minor amputation			
Did not undergo	1.11	0.82	1.48
Underwent	0.35	0.35	_
Major amputation			
Did not undergo	0.98	0.71	1.48
Underwent	_	-	_
Skin grafting			
Did not undergo	0.98	0.69	2.36
Underwent	0.88	0.53	0.99

Source: Research data.

Figure 1 shows the Kaplan-Meyer curve of survival of wounds in the lower limbs (LL). The survival function (t) is represented in the vertical axis and the survival time (T),

in days, in the horizontal axis. It indicates the likelihood of wound healing over a specific period of time.

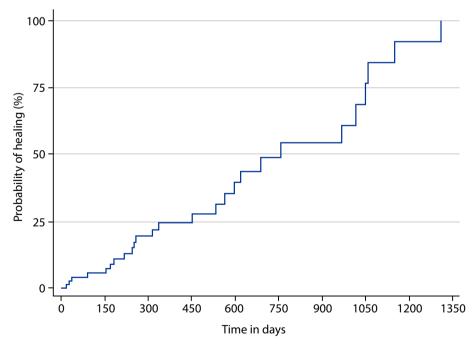
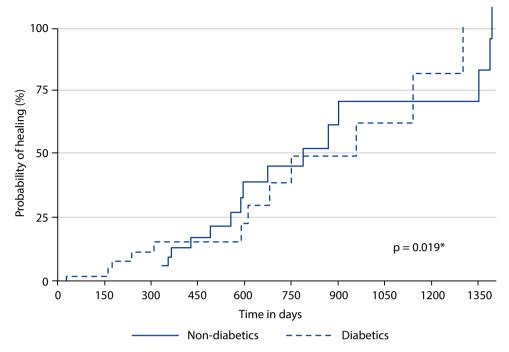


Figure 1 - Probability of healing of ulcer in the lower limbs

On the other hand, Figure 2 shows the probability of wound healing in diabetic and non-diabetic patients, with statistical significance for the Log-rank test (p = 0.019) in

group comparison. In up to 600 days, the wounds of 23% of the diabetic patients had healed, while 63% of non-diabetic patients had their wounds healed.



**Figure 2 -** Probability of ulcer healing in the lower limbs, comparing diabetic and non-diabetic individuals Note: \*p value for Log-rank test comparing diabetic and non-diabetic individuals.

Finally, Table 4 includes the unadjusted values of Hazard Ratio (HR) for healing according to the presence or absence of diabetes. There were no statistically significant differences in RH between the proposed variables, except

for the patients who presented venous ulcer in the group of non-diabetic patients, who had a lower probability of healing (HR = 0.13, 95% CI = 0.02- 0.97) compared to those without venous ulcers.

Table 4 – Gross Hazard Ratio CI95% for healing, not adjusted, in diabetic and non-diabetic patients

Variables -	Total Sample		Diabetics		Non-diabetics	
	HR*	IC95%**	HR*	IC95%**	HR*	CI 95%**
Age range (years)						
18-65*	-	-	-	-	=	-
> 65	1.05	0.47-2.32	0.81	0.26-2.56	1.49	0.50-4.45
ВМІ						
Not overweight*	-	-	-	-	-	-
Overweight	1.08	0.44-2.60	1.11	0.30-4.17	1.13	0.35-3.67
Education						
Incomplete secondary education to complete higher education *	-	-	-	-	-	-
Illiterate to complete primary education	1.10	0.45-2.70	0.82	0.25-2.68	1.25	0.27-5.80
Smoking						
Nonsmoker*	-	-	-	-	-	-
Smoker	0.99	0.23-4.32	1.87	0.24-14.78	0.50	0.06-3.97
Ex-smoker	0.60	0.25-1.44	0.35	0.08-1.63	0.76	0.25-2.32

Arterial ulcer						
Absence*	-	-	-	-	-	-
Presence	0.65	0.28-1.49	0.62	0.20-1.97	1.36	0.38-4.87
Venous ulcer						
Absence*	-	-	-	-	-	-
Presence	2.20	0.98-4.90	2.25	0.68-7.49	0.13	0,02-0,97
Neuropathic ulcer						
Absence*	-	-	-	-	-	-
Presence	0.57	0.22-1.42	0.89	0.29-2.77	-	-
Unna boot						
Did not use*	-	=	-	-	-	=
Used	1.40	0.64-3.04	1.01	0.13-7.84	0.48	0.15-1.54
Compressive therapy						
Did not use*	-	-	-	-	-	-
Used	2.13	0.99-4.61	2.53	0.33-19.64	1.14	0.32-4.09
Bypass						
Did not undergo*	-	-	-	-	-	-
Underwent	0.64	0.15-2.72	0.68	0.09-5.24	0.64	0.08-4.87
Angioplasty						
Did not undergo*	-	-	-	-	-	-
Underwent	0.34	0.10-1.14	0.18	0.02-1.41	0.82	0.18-3.67
Surgical debridement						
Did not undergo*	-	-	-	-	-	-
Underwent	0.45	0.13-1.50	0.24	0.03-1.89	1.08	0.24-4.83
Minor amputation						
Did not undergo*	-	-	-	-	-	-
Underwent	0.31	0.07-1.34	0.43	0.09-1.95	-	-
Major amputation						
Did not undergo*	-	-	-	-	-	-
Underwent	0.00	-	0.00	-	-	-
Skin grafting						
Did not undergo*	-	-	-	-	-	-
Underwent	0.90	0.37-2.13	0.77	0.10-6.00	0.42	0.14-1.21
C D L L						

Source: Research data.

 $Notes: \verb§+Hazard Ratio; \verb§+*Confidence intervals of 95\%. Confidence interval of 95\% in bold - Statistical significance.$ 

# DISCUSSION

The present study showed a higher percentage of female patients, over 65 years of age, low educational level and patients with chronic diseases. The probability of wound healing was significantly lower in the diabetic

group compared to the non-diabetic group. In addition, the lowest rate of healing occurred in the group of patients with venous ulcers compared to those without venous ulcers.

The mean age of study participants was 72 years. The higher prevalence of the elderly population in this study

is consistent with the situation in Brazil, a country that has undergone a process of intense demographic transition in recent years<sup>(11)</sup>. Concomitantly to this transition, there have also been changes in the nutritional and morbidity and mortality patterns of the population. As these diseases and chronic diseases have mostly affected individuals in advanced ages, an increase in the number of cases of wounds in the lower limbs is to be expected. This association was previously described in the literature<sup>(12)</sup>.

DM was the most significant CNCD in this study, as it was present in 61.54% of the study sample and its underlying metabolic effects may interfere with wound healing. According to the Brazilian Society of Diabetes<sup>(2)</sup>, population aging, sedentary lifestyle, higher incidence of diseases such as obesity and the longer survival of DM patients are factors that have contributed to the increase in the number of these individuals<sup>(2)</sup>. When uncontrolled, this disease can lead to several complications, such as neuropathy and vasculopathy, which alone or combined, are responsible for the onset of neuropathic ulcer<sup>(13)</sup>.

In the present study, 32.05% of the patients had neuropathic ulcers. These ulcers are foot wounds present in 4 to 10% of diabetics<sup>(6)</sup> and are considered a challenging problem because these wounds are slow to heal especially when there is no control of DM and when the patients are not continuously monitored by the multidisciplinary health team<sup>(6,13)</sup>.

As for ulcers of other etiologies, 48.72% of the patients had venous ulcers and 38.46% had arterial ulcers. The percentage of patients with venous ulcers was similar to the one obtained in the study by Afonso et al. (2013), 56%, whose objective was to characterize patients with chronic active ulcers, identifying the vascular pathology involved and the factors related to delay healing. However, in the present study, the percentage related to arterial ulcer was higher than that obtained by the referred authors, who found 18% of cases of this type of wound<sup>(14)</sup>. It is believed that the greater occurrence of wounds of ischemic etiology may be related to the fact that the health team is composed of several vascular surgeons, which would generate more referrals of patients with such wounds.

As for the healing rate, it was found that it decreases with increase in time, in days. For Borges (2008), healing is a complex process, which is influenced by systemic factors related to the general conditions of the individual, such as age, nutritional status and the presence of CNCD; and local factors, such as infection and the presence of necrotic tissue, which may prolong the process of wound healing<sup>(15)</sup>.

Statistical significance was observed in the highest

wound survival for the group of diabetic patients, that is, the time required for healing was higher in relation to the group of non-diabetic patients. It is known that in diabetic patients, the wound repair process may be impaired due to decreased collagen synthesis and angiogenesis. We also highlight the changes caused by atherosclerosis where there is lower tissue oxygenation and change in the protective sensitivity caused by disorders in peripheral innervation<sup>(15)</sup>.

In turn, prolonged healing time in diabetics may be related to the onset of other complications. These include infections, osteomyelitis and, consequently, amputation of lower limbs. Non-traumatic amputations often occur after the development of foot ulcers in patients with DM and they occur above the tarsal mean level - is associated with high mortality rates<sup>(6)</sup>.

As for infection, diabetic patients have inflammatory response disorders, which are associated with metabolic disorders in the body and limb anatomy aggravates the consequences of infection. Therefore, many patients must be hospitalized for surgical intervention and antibiotic therapy, which makes treatment even more expensive and impacts their quality of life<sup>(6)</sup>.

#### CONCLUSION

The presents study found that patients with diabetes are less likely to have their wounds healed compared to non-diabetic patients. These findings may assist nurses who frequently engage in health promotion activities and predict wound healing time in patients with diabetes. In addition, the aspects explained here emphasize the need for preventive care throughout life, especially in patients at higher risk of developing neuropathic ulcers or who have previously had these wounds or amputations.

One limitation of this study concerns the use of a convenience sample, as further studies on the subject are needed, especially with a random sample and longer follow-up of the patients. However, it is important to stress the methodological rigor of this study and its contribution to the literature, as it has a longitudinal design and such studies are still scarce in Brazil.

Regarding the contributions of this study, it is worth noting that knowledge of the wound healing time and of the factors that interfere in this process can contribute to improve nursing care, minimize the consequences of diseases such as DM, and positively impact treatment and the quality of life of the patients, in addition to reducing health system costs.

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