Revista Portuguesa de Diabetes. 2016; 11 (1): 10-13

Long-term Prognosis of Diabetic Patients with a First Foot Ulcer in a Portuguese Tertiary Care Unit

Prognóstico a Longo Prazo de Doentes com uma Primeira Úlcera de Pé Diabético numa Unidade Portuguesa de Cuidados Terciários

S. Garrido, A. Couto de Carvalho, R. Carvalho

Division of Endocrinology, Diabetes and Metabolism, Hospital de Santo António – Centro Hospitalar do Porto, Porto, Portugal

Abstract

Introduction: Diabetic foot ulcer (DFU) is a major cause of morbidity and mortality in diabetic patients. Our aim was to evaluate the 5-year outcome of patients with a first DFU and to analyze variables related with mortality.
Methods: Retrospective analysis of clinical data of patients with a first DFU attending the Diabetic Foot Clinic at Hospital de Santo António during 2008 with determination of outcomes (amputation and death) until December-2014.
Results: The study included 248 patients. The median age at presentation was 70 years and the median diabetes duration was 15 years. Ulcers were neuroischemic/ischemic in 62.5%. During the 5-year period, 31.9% (95% CI, 24.1-39.7) of the patients had at least one minor amputation and 23.7% (95% CI, 16.6-30.9) one major amputation. The 5-year all-cause mortality rate was 45.6% (95% CI, 39.3-51.8). Patients with neuroischemic/ischemic foot had higher mortality rate (p<0.001), as well as older patients (p<0.001) and those with longer diabetes duration (p=0.03). Other factors associated with higher mortality were ischemic heart disease (p=0.005), cerebrovascular disease (p<0.001), peripheral arterial disease (p<0.001) and hypertension (p=0.001).
Conclusion: DFU is associated with high 5-year rates of amputation and mortality, especially among older patients with longer diabetes duration, hypertension and established macrovascular disease.

Keywords: diabetic foot ulcer, diabetes duration, neuroischemic/ischemic foot, minor amputation, major amputation, mortality.

Resumo

Introdução: As úlceras de pé diabético são uma causa importante de morbi-mortalidade nos doentes com diabetes *mellitus*.
Objetivos: Avaliar os desfechos aos 5 anos dos doentes com primeira úlcera de pé diabético e analizar as variáveis associadas à mortalidade.
Métodos: Análise retrospetiva de dados clínicos dos doentes com primeira úlcera de pé diabético que recorreram à Consulta do Pé Diabético do Hospital de Santo António durante 2008, com determinação dos desfechos (amputação e morte) até dezembro-2014.
Resultados: Incluídos 248 doentes, 62,5% com pé neuroisquémico/isquémico, idade mediana à apresentação de 70 anos e duração mediana da diabetes de 15 anos. Durante os 5 anos de seguimento, 31,9% (IC 95%, 24,1-39,7) dos doentes foram submetidos a amputação *minor* e 23,7% (IC 95%, 16,6-30,9) a amputação *major*. A taxa de mortalidade aos 5 anos foi de 45,6% (IC 95%, 39,3-51,8). Os doentes com pé neuroisquémico/isquémico apresentaram uma taxa de mortalidade superior (p<0,001), assim como os doentes mais velhos (p<0,001) e aqueles com mais anos de diagnóstico de diabetes (p=0,03). Outros fatores associados a uma maior taxa de mortalidade foram: doença cardíaca isquémica (p=0,005), doença cerebrovascular (p<0,001), doença arterial periférica (p<0,001) e hipertensão (p=0,001).
Conclusão: As úlceras de pé diabético estão associadas a uma elevada taxa de amputação e mortalidade aos 5 anos, especialmente entre indivíduos mais velhos, maior duração da diabetes, hipertensão arterial e doença macrovascular estabelecida.

Palavras-chave: úlcera de pé diabético, duração da diabetes, pé neuroisquémico/isquémico, amputação *minor,* amputação *major,* mortalidade.

> INTRODUCTION

Diabetic foot ulcers (DFU) are a common and challenging complication of diabetes, with a lifetime risk of its development as high as 25%. [1] They are an important cause of morbidity and mortality, determining an even higher risk of all-cause mortality than that of patients with diabetes and no history of DFU. [2,3] There are relatively few studies on long-term outcome of patients with a first DFU and we lack Portuguese studies. Such evidence would be useful to monitor care and hopefully improve management of these patients. The present study aims to evaluate the 5-year outcome of Portuguese diabetic patients with a first DFU, concerning amputation and all-cause mortality, and to analyze the clinical and demographic variables related with mortality.

CORRESPONDÊNCIA

Susana Garrido
Hospital de Santo António, Centro Hospitalar do Porto
Porto - Portugal
Tel.: +351 : 222 077 500
E-mail: scggarrido@gmail.com

Recebido/Received: 18/01/2016; Aceite/Accepted: 04/03/2016.

> MATERIAL AND METHODS

We have conducted a retrospective data analysis of all patients with a first DFU attending the Diabetic Foot Clinic of Hospital de Santo António/Centro Hospitalar do Porto, a Portuguese tertiary care unit, during 2008. Data on outcome (mortality, minor and major amputation) were collected from hospital records and national mortality register up to December 2014. Cause of death was not ascertained. For determination of amputation rate we included only patients with history of amputation and/or available clinical records for the all 5-year follow-up period. Patients with history of previous DFU and those with missing relevant data were excluded from the analysis.

Demographic variables obtained included gender and age at first clinic attendance. Clinical data included type of diabetes, duration of diabetes, HbA1c, metabolic and microvascular complications (diabetic neuropathy, diabetic nephropathy and diabetic ophthalmopathy), macrovascular disease (ischemic heart disease, peripheral artery disease, cerebrovascular disease), hypertension, dyslipidemia and smoking habits (smoker/ex-smoker vs non-smoker). Peripheral neuropathy was assessed through Semmes-Weinstein monofilament testing and peripheral vascular disease was considered present if *dorsalis pedis* and posterior tibial pulses were absent by palpation in the affected limb. Based on this, ulcers were classified as neuropathic or neuroischemic/ischemic (grouped due to the rarity of purely ischemic ulcers identified). Minor amputation and major amputation was defined as below or above the ankle, respectively. Duration of diabetes was self-reported, as were diabetic nephropathy, diabetic ophthalmopathy, ischemic heart disease, cerebrovascular disease, hypertension and dyslipidemia. HbA1c concentrations were measured using Siemens DCA 2000 (Siemens Healthcare Diagnostics, Deerfield, IL) (immunoassay).

Statistical analysis was performed using SPSS for Windows v20.0, through descriptive and inferential statistics with Chi-squared test and Mann–Whitney U test, as appropriate. Values of $p \leq 0.05$ were considered statistically significant.

> RESULTS

During 2008, a total of 248 patients with first DFU were seen at the Diabetic Foot Clinic. The male to female ratio was 1.2:1 and the median age at presentation was 70.0 years old (interquartile range, IQR, 61.0-76.5). Most of the patients had type 2 diabetes (94.4%). The median diabetes duration was 15 years (IQR, 8.0-22.0) and the median HbA1c was 8.0% (IQR, 6.8-9.9). Ulcers were exclusively neuropathic in 37.5% of patients and neuroischemic/ischemic in 62.5% (Table I).

During the 5-year period of follow up, 44.8% (95% CI, 36.6-53.0) of patients were submitted to amputation (65/145); 31.9% (95% CI, 24.1-39.7) had at least one minor amputation (45/141) and 23.7% (95% CI, 16.6-30.9) had at least one major amputation (33/139). Minor amputations were more frequent in neuroischemic/ischemic foot ulcers (75.6%, p 0.04) and major amputations happened almost exclusively in neuroischemic/ischemic foot ulcers (97.0%, p <0.001). The 5-year all-cause mortality rate was 45.6% (95% CI, 39.3-51.8) for the entire group (113/248). Patients with neuroischemic/ischemic foot had a higher mortality rate than those with neuropathic foot [54.8% (95% CI, 46.9-62.8) vs 29.0% (95% CI, 20.6-39.6), p<0.001]. Patients who died during the 5 year period were also older at presentation [median age 75.0 years (IQR, 69.0-81.0) vs 64 years (IQR, 56.0-72.0); p<0.001] and had longer diabetes duration [15 years (IQR, 10.0-29.5) vs 13 years (IQR, 5.0-20.0); p=0.03]. Other factors associated with mortality were: ischemic heart disease (p=0.005), cerebrovascular disease (p<0.001), peripheral arterial disease (p<0.001) and hypertension (p 0.001). None of the other clinical and demographic variables tested were related with this outcome (Table 1).

> DISCUSSION

DFU are a common complication of diabetes and it can be seen as the tip of an iceberg, as it is often a sign of overall poor health and prognosis. In our study, a first DFU was associated with a 5-year amputation rate of 44.8% and a mortality rate of 45.6%, in a population that included mostly elderly men with long standing and poorly controlled diabetes with several comorbidities. The same population, mostly elderly males with long-standing diabetes and a poor health status with an increasing prevalence of peripheral artery disease and neuroischemic foot ulcers, was also found in the pioneering Eurodiale study where over 1,000 diabetic foot ulcer patients referred to 14 different European hospitals were evaluated. [4,5] This increasing prevalence of diabetic foot ulceration in patients with peripheral artery disease is a common pattern recognized by several other observational studies. [3,6]

Overall, diabetic patients have a 30 times greater lifetime risk of having an amputation than patients without diabetes. [7] Few studies have assessed long term outcome of patients presenting with new-onset DFU. Our

Table I - Demographic and clinical characteristics of first diabetic foot ulcer patients according to their survival status.

	Total (n=248)	Surviving group (n=136)	Non-surviving group (n=112)	*p*
Gender				
Female	114 (46.0%)	56 (49.1%)	58 (50.9%)	0.106
Male	134 (54.0%)	80 (59.7%)	54 (40.3%)	
Age (years)*	70.0 (61.0-76.5)	64.0 (56.0-72.0)	75.0 (69.0-81.0)	<0.001
Type of diabetes				
Type 1	14 (5.6%)	11 (78.6%)	3 (21.4%)	0.062
Type 2	234 (94.4%)	124 (53.0%)	110 (47.0%)	
Duration of diabetes (years)*	15.0 (8.0-22.0)	13.0 (5.5-20.0)	15.0 (10.0-29.5)	0.03
HbA1c (%) *	8.0 (6.8-9.9)	7.9 (6.8-10.6)	8.0 (6.9-9.7)	0.99
Hypertension				
Yes	202 (83.5%)	100 (49.3%)	102 (50.7%)	0.001
No	40 (16.5%)	32 (80.5%)	8 (19.5%)	
Dyslipidemia				
Yes	156 (67.0%)	79 (50.6%)	77 (49.5%)	0.101
No	77 (33.0%)	48 (62.3%)	29 (37.7%)	
Smoking habits				
Smoker/Ex-smoker	57 (25.8%)	35 (61.4%)	22 (38.6%)	0.37
Non-smoker	164 (74.2%)	89 (54.3%)	75 (45.7%)	
Diabetic Neuropathy				
Yes	221(92.5%)	126 (57.0%)	95 (43.0%)	0.05
No	18 (7.5%)	6 (33.3%)	12 (66.7%)	
Diabetic Retinopathy				
Yes	123(55.7%)	68 (55.3%)	55 (44.7%)	0.78
No	98 (44.3%)	55 (56.1%)	43 (43.9%)	
Diabetic Nefropathy				
Yes	57 (28.5%)	26 (45.6%)	31 (54.4%)	0.12
No	143 (71.5%)	82 (57.3%)	61 (42.7%)	
Ischemic heart disease				
Yes	52 (23.3%)	20 (38.5%)	32 (61.5%)	0.005
No	171 (76.7%)	103 (60.2%)	68 (39.8%)	
Cerebrovascular disease				
Yes	67 (28.5)	23 (34.3%)	44 (65.7%)	<0.001
No	168 (71.5%)	106 (63.1%)	62 (36.9%)	
Peripheral artery disease				
Yes	155 (62.5%)	70 (45.2%)	85 (54.8%)	<0.001
No	93 (37.5%)	65 (69.9%)	28 (30.1%)	
Diabetic foot classification				
Neuropathic Foot	93 (37.5%)	66 (71.0%)	27 (29.0%)	<0.001
Neuroischemic/Ischemic Foot	155 (62.5%)	70 (45.2%)	85 (54.8%)	

* Data expressed as median and interquartile range.

5-year amputation rate [44.8% (95% CI, 36.6-53.0)] was much higher than that reported by other studies. Moulik *et al*. examined the 5-year outcome of 185 patients with new-onset DFU and reported an amputation rates of 19% [8] and Ramsey *et al.* calculated a 15.6% 3-year amputation rate among 514 patients also with first DFU. [9] These differences may be explained by the higher prevalence of neuroischemic foot ulcers in our series, as they are a known risk factor for subsequent amputation. Likewise, though not addressed in this study, the high amputation rate could probably also reflect a referral bias, since more patients are being treated exclusively in primary care settings and only the patients with peripheral artery disease and/or moderate to severe infection

are being referred to our tertiary clinic. In support to this hypothesis, similar amputations rates have only been described when diabetic patients hospitalized for acute diabetic foot syndromes are included. [10]

In our study, patients with first DFU were found to have a high 5-year mortality rate [45.6% (95% CI, 39.3-51.8)], in agreement with previous observations regarding new-onset DFU (mortality rates reported between 36.4 and 44.0%). [8,11] As expected, the prognosis was worse among older patients with longer diabetes duration, history of macrovascular disease and hypertension. The excess risk of mortality found can be partly explained by the increased CVD risk observed in these DFU patients. Other factors, like greater diabetes burden and non-cardiovascular complications of foot ulceration, may also contribute for the excess mortality observed. [2] Addressing total burden of disease and preventing further deterioration of general health status of DFU patients should be one of our major efforts.

To our knowledge, this is the first Portuguese study concerning exclusively long-term outcome of diabetic patients with new-onset DFU. We included only patients with first DFU to avoid overestimation of disease severity that could occur if we also included recurrent DFU cases. Despite being a retrospective study and its many bias, our outcome results may be regarded as accurate, since we reviewed all hospital records and the national mortality register.

> CONCLUSION

In summary, this study confirms the great morbidity, brought by amputation, of patients with DFU, as well as the associated high mortality. This points out the need for an aggressive approach to new onset DFU patients, through a careful follow-up and management by multidisciplinary teams. In this population, addressing foot problems is essential, but we also should not forget to engage control of cardiovascular risk factors and other comorbid conditions. Hopefully, in the future, we will have new and prospective data from the multicentric Portuguese Registry of Patients with Diabetic Foot Infection (RENAPEDI) to better understand all prognosis predictive factors. <

Acknowledgements

The authors thank T. Pereira, M. Ferreira, A.M. Silva, S. Teixeira, A. Giestas, H. Neto, J. Martins, J. Muras, I. Gonçalves, C. Amaral, C. Freitas, R. Guimarães and S. Pinto, also members of the Diabetic Foot Clinic "Dra. Beatriz Serra" and A. Cruz, A. Serra, A. Silva, J. Correa, J. Vale, J. Cardoso, M. Laranjo, M. Gonçalves, M. Barreira, M. Fernandes, R. Rodrigues, R. Pereira, V. Tavares, medical students at the Instituto de Ciências Biomédicas Abel Salazar – University of Porto, who contributed to the data collecting process.

REFERENCES

1. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005; 293(2): 217-28.
2. Brownrigg JR, Davey J, Holt PJ, Davis WA, Thompson MM, Ray KK, et al. The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis. Diabetologia. 2012; 55(11): 2906-12.
3. Martins-Mendes D, Monteiro-Soares M, Boyko EJ, Ribeiro M, Barata P, Lima J, et al. The independent contribution of diabetic foot ulcer on lower extremity amputation and mortality risk. J Diabetes Complications. 2014; 28(5): 632-8.
4. Schaper NC. Lessons from Eurodiale. Diabetes Metab Res Rev. 2012; 28 Suppl 1: 21-6.
5. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007; 50(1): 18-25.
6. Li X, Xiao T, Wang Y, Gu H, Liu Z, Jiang Y, et al. Incidence, risk factors for amputation among patients with diabetic foot ulcer in a Chinese tertiary hospital. Diabetes Res Clin Pract. 2011; 93(1): 26-30.
7. Moxey PW, Gogalniceanu P, Hinchliffe RJ, Loftus IM, Jones KJ, Thompson MM, et al. Lower extremity amputations--a review of global variability in incidence. Diabet Med. 2011; 28(10): 1144-53.
8. Moulik PK, Mtonga R, Gill GV. Amputation and Mortality in New-Onset Diabetic Foot Ulcers Stratified by Etiology. Diabetes Care. 2003; 26(2): 491-4.
9. Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care. 1999; 22(3): 382-7.
10. Ghanassia E, Villon L, Thuan dit Dieudonné JF, Boegner C, Avignon A, Sultan A. Long-term outcome and disability of diabetic patients hospitalized for diabetic foot ulcers: a 6.5-year follow-up study. Diabetes Care. 2008; 31(7): 1288-92.
11. Winkley K, Sallis H, Kariyawasam D, Leelarathna LH, Chalder T, Edmonds ME, et al. Five-year follow-up of a cohort of people with their first diabetic foot ulcer: the persistent effect of depression on mortality. Diabetologia. 2012; 55(2): 303-10.
12. Iversen MM, Tell GS, Riise T, Hanestad BR, Østbye T, Graue M, et al. History of foot ulcer increases mortality among individuals with diabetes: ten-year follow-up of the Nord-Trøndelag Health Study, Norway. Diabetes Care. 2009; 32(12): 2193-9.