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ORIGINAL ARTICLE

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Anxiety and/or depression: which symptoms contribute to adverse clinical outcomes after amputation?

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ABSTRACT

Background: One of the most serious complications of diabetes mellitus (DM) is a diabetic foot ulcer (DFU), with lower extremity amputation (LEA).

Aims: This study aims to explore the role of anxiety and depression on mortality, reamputation and healing, after a LEA due to DFU.

Methods: A sample of 149 patients with DFU who underwent LEA answered the Hospital Anxiety and Depression Scale and a sociodemographic and clinical questionnaire. This is a longitudinal and multicenter study with four assessment moments that used Cox proportional hazards models adjusted for demographic and clinical variables.

Results: Rate of mortality, reamputation and healing, 10 months after LEA were 9.4%, 27.5% and 61.7%, respectively. Anxiety, at baseline, was negatively associated with healing. However, depression was not an independent predictor of mortality. None of the psychological factors was associated with reamputation.

Conclusion: Results highlight the significant contribution of anxiety symptoms at pre-surgery, to healing after a LEA. Suggestions for psychological interventions are made.

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Introduction

About 13% of the adult Portuguese population have diabetes mellitus (DM) (Portuguese Diabetes Observatory, 2015). Diabetic foot lesions are a consequence mainly of chronic diabetic complications such as neuropathy and peripheral vascular disease (Bakker et al., 2016). Most diabetes-related lower extremity amputations (LEA) occur after the failure of a diabetic foot ulcer (DFU) to heal due to uncontrolled infection and/or ischemia (Monteiro-Soares et al., 2015). Currently, it is estimated that every 20 seconds a LEA is performed somewhere in the world due to DM (Boulton et al., 2005; International Diabetes Federation, 2017). DFU also increases dramatically the rates of mortality and morbidity in this population (Moxey et al., 2011). Portugal has the highest rate of DM in the European Union (OECD, 2016) with a growing trend due to specific characteristics of the Portuguese population (de Sousa-Uva et al., 2016). DM, is, therefore, considered a public health problem. However, to our knowledge, there are no prospective studies in Portugal reporting the rates of clinical outcomes after a LEA in patients with diabetes mellitus type 2 (DMT2) and DFU. In Portugal, the National Health Service (NHS) co-exists with two other health subsystems. The NHS is a universal service, comprehensive and almost free, financed mainly through individual's taxes. All residents are covered, irrespective of their socioeconomic, employment or legal status. Also, special health insurance schemes cover particular professions or sectors; these are called "health subsystems" and can be either public (e.g. for civil servants) or private (e.g. banking sector). Private Voluntary Health Insurance is supplementary and speeds up access to elective hospital treatment and ambulatory consultations increasing also the choice of a provider. Regardless of the health care system, all patients are attended in ambulatory consultations and received elective treatment when at risk of amputation (OECD/European Observatory on Health Systems and Policies, 2017).

In general, after a LEA, there is an increased risk of reamputation, nonhealing wounds and death (Desmond & Gallagher, 2008; Jupiter et al., 2016; López-de-Andrés et al., 2019; Thorud, Jupiter, et al., 2016; Thorud, Plemmons, et al., 2016). Research has focused on the role of depression as a diagnosed disorder (Al-Smadi & Gharaibeh, 2019; Ismail et al., 2007; Katon et al., 2005; Vedhara et al., 2010; Winkley et al., 2012), and regarding depressive symptoms (Gonzalez et al., 2010; Iversen et al., 2009), on clinical outcomes, such as mortality, healing, and risk of ulceration or re-ulceration, in patients with a new foot ulcer. In addition, depression has been identified as a significant predictor of reduced life expectancy in patients with DM (Katon et al., 2005; Nowakowska et al., 2019), in patients with a history of ulcers (Ismail et al., 2007; Shrestha et al., 2019) and patients-with their first foot ulcer (Al-Smadi & Gharaibeh, 2019;

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Ismail et al., 2007; Iversen et al., 2009; Katon et al., 2005; Winkley et al., 2012). Depression is also a risk factor for ulceration (Ismail et al., 2007; Vas & Papanas, 2020) and for a delay in ulcer healing (Shrestha et al., 2019; Vedhara et al., 2010). However, there is a bidirectional relationship between depression and diabetes. Neuroendocrine signaling, through hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, is thought to cause or exacerbate depression in patients with diabetes (Downs & Faulkner, 2015). Interestingly, in the only study, the authors know of, which assessed the role of depression symptoms in mortality after LEA, no association was found between depressive (and anxiety) symptoms and mortality (Singh & Prasad, 2016).

Regarding anxiety symptoms, there is a strong consensus on the association between stress and delayed wound healing (Cacha et al., 2019; Herbert & Cohen, 1993) in surgical ulcers (Goodwin et al., 2013; Walburn et al., 2009) and chronic leg wounds (Goodwin et al., 2013; Gouin & Kiecolt-Glaser, 2011; Walburn et al., 2009). Toxic stress affects the HPA axis and contributes to inflammation, an important biological contributor to the pathogenesis of DM and its complications (Downs & Faulkner, 2015). Also, stress can trigger more prolonged negative emotional states (Pereira et al., 2019), which affect physiological processes, attitudes and behaviors which, in turn, affect and influence health outcomes (Guo & DiPietro, 2010; Robinson et al., 2017).

However, to the best of our knowledge, no longitudinal study has focused on the role and influence of anxiety and depression symptoms, in predicting clinical outcomes after LEA. Understandably, emotional symptoms are common in patients with DM and, especially, after a LEA (Desmond & Gallagher, 2008; Gallagher et al., 2019), but it is unclear whether there is any impact on short (1-month) and long-term (1-year) clinical outcomes as well as what is the differential role of depression and anxiety symptoms.

Clark and Watson's Tripartite Model (Clark and Watson 1991), explains the association between anxiety and depression in adults, suggesting that anxiety and depression share an underlying similarity, but are also comprised of unique characteristics. Anxiety and depression share a common component of negative affect, which accounts for symptom overlap and comorbidity. Negative affect represents the extent to which an individual feels upset or unpleasantly engaged, rather than at peace. However, symptoms can be differentiated by two constructs: positive affect and physiological hyperarousal. Positive affect refers to the pleasurable engagement with the environment and encompasses mood states and feelings such as energetic, pleasant, active and enthusiastic. Physiological hyperarousal includes somatic tension and symptoms of shortness of breath, dizziness, light-headedness and dry mouth. Clark and Watson's model posits that individuals with symptoms or a diagnosis of depression tend to exhibit low levels of positive affect and high levels of negative affect, whereas individuals with anxiety disorders tend to exhibit high levels of physiological arousal as well as high levels of negative affect. The differentiation of anxiety and depression symptoms has been improved, emphasizing the importance of negative affect globally and focusing on the specific and unique symptoms of each construct. Therefore, in the present study, both symptoms are treated differently, allowing a more complete picture of the impact of these symptoms on clinical outcomes.

The present study is the first to examine, in a multicenter and longitudinal design study, not only the prevalence rates of clinical outcomes following a LEA but also the association of depression and anxiety symptoms with time of death, reamputation and healing in patients with DMT2 and DFU, after a LEA. We hypothesized that depression symptoms will be positive predictors of mortality and anxiety symptoms will be negative predictors of healing and positive predictors of reamputation. The results will highlight not only which emotional symptoms contribute to each clinical outcome, but also, when they are likely to contribute the most, from the pre-surgery to 10 months after surgery.

Methods

Sample

Two hundred and thirty-nine patients proposed for amputation surgery were identified by the health professionals' team who collaborate with this study. Of these, 206 gave their informed consent and 33 were excluded (seven refused participation; five had their surgeries canceled; two died before surgery; one patient was in the intensive care unit; two participants were transferred to a different hospital; two participants showed major hearing loss and 14 received emergency amputations and were excluded due to procedural reasons). Patients were enrolled consecutively and were invited to collaborate in the study when they were informed that they would undergo an amputation surgery. The patients were assessed on average two days (SD 3.8) before the surgery and half of the sample was assessed 24 hours before the surgery (1–21 days, min–max). After surgery, 149 patients participated in the study and were included in the analysis. Table 1 shows the demographic, clinical and psychological characterization of the sample.

The inclusion criteria included being an adult patient with DMT2 and with a DFU proposed for LEA. Having a history of diagnosed severe psychiatric disorder (self-reported or reported in the patient's medical records such as psychosis or dementia), not being able to understand written information or providing verbal responses were exclusion criteria; amputations for reasons other than those related to the DFU were excluded.

Design

This study had a prospective design with four assessment moments: baseline (just before LEA: T0), one (T1), six (T2) and 10 months (T3) after surgery and enrolled patients with DMT2 and DFU who were admitted to the hospital for LEA. In this study, amputation was defined as a resection of a segment of a limb through a bone. The study was conducted at six major hospitals from the North of Portugal, within Multidisciplinary Diabetic Foot Clinics and/or Departments of Vascular Surgery. Data collection took place between June 2013 and January 2016.

Measures

Assessment interviews were conducted face-to-face by a health psychologist. Participation was voluntary and all participants filled an informed consent form. A psychological assessment was performed at four different moments (T0, T1, T2 and T3).

Sociodemographic variables

At baseline (during the hospitalization that preceded the surgery), data regarding socio-demographic and clinical information were recorded using a questionnaire developed for the present study. Socio-demographic information included age and gender.

Clinical variables

The clinical questionnaire included diabetes-specific information concerning the duration of DMT2, type of diabetic foot (pure neuropathic versus neuroischemic), ambulatory capacity (with/without), number of other DM associated complications, level of index amputation (minor or major), history of previous amputations, 1st reamputation date. Major LEA was defined as above the ankle joint. Minor extremity amputations were all the others below the ankle joint.

Clinical outcomes evaluated in this study were: time to death, time to reamputation, and time to lesion healing, at 1 month (T1), six (T2) and 10 months (T3) after LEA. All-cause mortality and time-of-death were obtained from hospital records and by phone contact when patients missed follow-up scheduled appointments. All causes of mortality were considered as an event. Reamputation rate and time-to-first-reamputation were retrieved from medical records. Time-free-of-reamputation was calculated from the date of the index amputation to the first reamputation. This event was defined as an amputation that occurred when the patient was submitted to another amputation beyond the first schedule LEA. Lesion healing was defined as an intact skin, meaning complete epithelization of a previously ulcerated site. No fixed date-of-healing was recorded due to the time interval between follow-up appointments. Therefore, this event was registered as a nominal variable (yes/no) during different interval times (from between T0 and T1, between T1 and T2 and between T2 and T3). The follow-up assessment moments were determined according to clinical criteria, since, one month after surgery, it is expected that, in a best-case scenario, the lesion to be already healed; six months after surgery, the patient should have started rehabilitation and physiotherapy treatments; and 10 months after surgery, patients would be fully rehabilitated and independent with foot orthoses or a lower limb prosthesis. To limit follow-ups' drop-out, the last evaluation was anticipated to 10 months although initially planned to be carried out at 12 months.

Anxiety and depression

To measure anxiety and depression symptoms, the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) was used. HADS is a self-report scale of 14 items rated on a four-point Likert scale (range 0–3), assessing anxiety (HADS-A: seven items) and depression symptoms (HADS-D: seven items). The total score of each scale is the sum of the seven items (ranging from 0 to 21). Higher scores indicate higher levels of anxiety and depression symptoms, respectively. In this study, Cronbach's alpha for HADS-A was 0.86 and 0.88 for HADS-D. This instrument has been validated in Portuguese patients with diabetes (Pais-Ribeiro et al., 2007) and amputees (Desmond & Maclachlan, 2005) and is a widely used measure in clinical practice in hospital settings, assessing depression and anxiety symptoms in a brief, quick and easy way.

Statistics

Dropout patients were compared with the study sample at T0, using Pearson's Chi-square (categorical variables) and independent *t*-tests (continuous variables). A Pearson correlation and Pearson's Chi-square were performed to analyze the associations between demographic, clinical and psychological variables with the three outcomes, as well as anxiety and depressive symptoms multicollinearity. Single-variable Cox proportional hazard models (Cox, 2018) were used to investigate associations between demographic, clinical and psychological variables from all time points, and all three outcome variables (1 – time from presentation to death, 2 – time from presentation to reamputation and 3 – time from presentation to healing). Multivariable Cox models were also constructed, including variables of known prognostic value and clinical relevance (age and gender), and variables that emerged as significant predictors in univariate analyses. Variables with $p < 0.05$ were included in Cox models and missing data were not imputed. Accordingly, the predictive ability of all explanatory variables was measured by adjusted hazard ratios (HRs) and its confidence intervals. HR and the overall survival rates (calculated using the Kaplan–Meier estimator) were used (Kaplan & Meier, 1958). The beginning of follow-up corresponded to the date of the amputation surgery. Patients were censored (right) at the time of loss to follow-up or at the end of the study for all outcome variables. Patients who died without having a reamputation were censored (right) at that time for the outcome variable "time to reamputation". In addition to right censoring, interval censoring was also found in the analyses of the outcome variable "time to healing". This type of censoring occurs when it is not known the exact time that event occurs, but only the interval in which it occurred. Therefore, for the analyses, a proportional hazards model was used for interval-censored data, proposed by Pan (1999) which is implemented in the R

Table 1. Demographic, clinical and psychological characterization.

	Total sample T0 ($N=149$)	T1 ($n=144$)	T2 ($n=107$)	T3 ($n=96$)	Dropout after T0 ($n=57$)
Demographic variables					
Age (mean (SD))	65.5 (10.7)	65.6 (10.7)	64.7 (10.9)	63.7 (10.7)	67.4 (11.3)
Male gender (*n* (%))	105 (70.5%)	102 (70.8)	74 (69.2)	71 (74.0)	47 (75.8)
Clinical variables					
Ambulatory capacity (y)	93 (62.4%)	89 (61.8)	70 (65.4)	64 (66.7)	32 (56.1)
Duration diabetes (months) (mean (SD))	223.7 (140.5)	223.6 (141.1)	214.2 (144.6)	216.8 (142.3)	215.2 (133.6)
Type of foot (neurolsq) (*n* (%))	114 (76.5%)	110 (76.4)	80 (74.8)	69 (74.9)	42 (67.7)
Level of index amputation: minor	119 (79.9%)	116 (80.6)	85 (79.4)	77 (80.2)	
Number of complications DM (mean (SD))	2.99 (0.94)	3.01 (0.93)	3.0 (0.9)	3 (1.0)	2.1 (0.98)
History of previous amputation (y) (*n* (%))	69 (46.3%)	69 (47.9)	48 (44.9)	45 (46.9)	41 (66.1)*
Psychological variables					
Anxiety symptoms score (mean (SD))	11.93 (5.02)	9.24 (5.42)	8.39 (5.36)	7.74 (4.91)	10.9 (5.63)
Depression symptoms score (mean (SD))	9.44 (5.76)	9.82 (5.79)	8.07 (5.69)	7.85 (6.13)	9.68 (6.42)

Continuous variables are presented as mean (SD); categorical variables are presented as *n* (%). Anxiety and depression symptoms assessed by HADS, Hospital Anxiety and Depression Scale scores.
T0: baseline; T1: one month after surgery; T2: six months after surgery; T3: 10 months after surgery; DM: diabetes mellitus; (y): yes.
*$p < 0.05$.

package intcox. All analyses were performed using R software (version 3.2.5).

Ethics

Informed consent was obtained in accordance with the ethical standards of the Helsinki Declaration of 1975, and the study was approved by the ethics committees of all hospitals where data collection took place (060/13(030-DEFI/059-CES)).

Results

Participant's characteristics

One hundred and forty-nine patients with DMT2 and DFU treated with LEA were included in the study and followed for 10 months following surgery (ranging between 194 and 652 days). At baseline, 69 patients had already a previous LEA (46.3%), from those, 14 (20.3%) had a major LEA and 55 (79.7%) had minor amputations. Patients who drop out during the study follow up were compared with the study sample at T0 and no differences in sociodemographic and clinical variables were found, except for the history of previous amputation, i.e. patients who did not complete the study had less or no history of previous amputations ($\chi^2 = 0.043$, $p < 0.05$) (Table 1).

Mortality, reamputation and healing rate

The cumulative rates were calculated from the cumulative incidence of clinical outcomes at 1, 6 and 10 months. Fourteen patients died during the study – a mortality rate of 9.4%; 41 patients underwent a reamputation over the course of the study – a reamputation rate of 27.5%; and 92 patients achieved a healed lesion – a healing rate of 61.7%. Clinical outcome rates at each of the follow-up assessments are presented in Table 2, showing the short (at 30 days) and a long-term (10 months) post-operative rate. Higher rates of mortality and healing were registered between T1 and T2 (9.3% and 53.3%, respectively). Reamputation rates were highest between T0 and T1 (14%).

Correlations between demographic, clinical and psychological predictors, and outcomes

Healing was positively associated with neuropathic foot ($\chi^2(1) = 0.459$, $p < 0.05$), and negatively associated with anxiety symptoms at T1 ($r = -0.186$, $p < 0.05$), and T3 ($r = -0.315$, $p < 0.01$). Depression symptoms at T0 were positively associated with mortality ($r = 0.184$, $p < 0.05$), and duration of DM diagnosis ($r = 0.163$, $p < 0.05$) and anxiety symptoms at T3 ($r = 0.272$, $p < 0.01$) were positively associated with reamputation. There were no associations between the other demographic and clinical variables and the three outcomes.

Predictors of mortality

In univariate analysis, symptoms of depression at T0 were associated with death (HR 95% CI: 1.11, 1.01–1.21, $p < 0.05$), but after adjusting for gender and age, in Cox regression, they were no longer significant predictors (Table 3).

Predictors of reamputation

In the univariate analysis, three clinical variables were significant predictors at baseline, but after adjusting for gender and age, ambulatory capacity (HR 95% CI: 0.67, 0.35–1.29, $p < 0.05$), duration of DM diagnosis (HR 95% CI: 1.00, 1.00–1.004, $p < 0.05$) and number of DM complications (HR 95% CI: 1.36, 0.91–2.02, $p < 0.05$), were no longer significant predictors (Table 3).

Predictors of healing

In the univariate analysis, anxiety symptoms at T2 and T3 were associated with healing. In Cox regression analysis, after adjusting for gender and age, these associations were

Table 2. Short- and long-term non-cumulative rates of all-causes mortality, reamputation and healing.

Outcome variables	Between T0 and T1 (n = 144)	Between T1 and T2 (n = 107)	Between T2 and T3 (n = 96)	Total sample (N = 149)
Mortality (n (%))	0	10 (9.3%)	4 (4.2%)	14 (9.4%)
Reamputation (1st) (n (%))	20 (14%)	14 (13.1%)	7 (7.3%)	41 (27.5%)
Healing (n (%))	12 (8.3%)	57 (53.3%)	23 (24%)	92 (61.7%)

Between T0 and T1: between baseline assessment to the first month after surgery; between T1 and T2: between the first and the sixth month after surgery; between T2 and T3: between the sixth and tenth month after surgery.

Table 3. Association of variables with healing, reamputation and mortality after a LEA.

	Healing (n = 92)		Reamputation (n = 41)		Mortality (n = 14)	
	Univariate HR (95% CI)	Multivariate HR OR (95% CI)	Univariate HR (95% CI)	Multivariate HR OR (95% CI)	Univariate HR (95% CI)	Multivariate HR OR (95% CI)
Demographic variables						
Age	1.00 (0.98–1.02)	1.00 (0.99–1.00)	1.001 (0.97–1.04)	1.001 (0.97–1.04)	1.04 (0.99–1.09)	1.03 (0.97–1.09)
Gender						
M	1	1			1	1
F	0.67 (0.41–1.07)	0.99 (0.90–1.09)	1.42 (0.74–2.71)	1.42 (0.74–2.71)	0.64 (0.17–2.29)	0.39 (0.10–1.49)
Clinical variables						
Ambulatory capacity						
0	1			0.67 (0.35–1.29)	1	
1	1.09 (0.71–1.67)		0.67 (0.35–1.29)		0.81 (0.28–2.35)	
Duration diabetes (months)	1.00 (0.999–1.001)		1.00 (1.00–1.004)	1.00 (1.00–1.004)	1.00 (0.99–1.01)	
Type of foot						
0	1		1		1	
1	1.47 (0.94–2.31)		0.94 (0.45–1.96)		0.54 (0.12–2.40)	
Level index amputation						
Minor	1		1		1	
Major	1.23 (0.62–2.46)		0.75 (0.22–2.57)		0.63 (0.08–5.21)	
Number complications	0.91 (0.73–1.14)		1.36 (0.91–2.02)	1.36 (0.91–2.02)	0.68 (0.40–1.15)	
History of previous amputation						
0	0.69 (0.43–1.06)		1.03 (0.56–1.91)		0.86 (0.30–2.46)	
1						
Psychological variables						
Anxiety symptoms						
T0	0.99 (0.95–1.03)	0.96 (0.95–0.97)*	1.04 (0.98–1.11)		1.04 (0.94–1.16)	
T1	0.97 (0.92–1.01)	1.00 (0.98–1.02)				
T2	0.96 (0.92–0.99)*	1.04 (1.00–1.08)				
T3	0.94 (0.89–0.98)*	1.02 (0.99–1.00)				
Depression symptoms						
T0	0.98 (0.94–1.02)		1.03 (0.98–1.08)		1.11 (1.01–1.21)*	1.06 (0.93–1.21)
T1	0.98 (0.93–1.02)					1.02 (0.89–1.17)
T2	0.98 (0.94–1.02)					1.08 (0.89–1.33)
T3	0.97 (0.92–1.004)					1.003 (0.86–1.17)

HR: hazard ratio; OR: odds ratio; CI: confidence interval; M: male; F: female; ambulatory capacity: 0 = no, 1 = yes; type of foot: 0 = neuropathic; 1 = neuroischemic; history of previous amputation: 0 = no; 1 = yes; T0: baseline; T1: one month after surgery; T2: six months after surgery; T3: 10 months after surgery.
*$p < 0.05$.

lost. However, anxiety symptoms at T0 were significant predictors of healing (HR 95% CI: 0.96, 0.95–0.97, $p < 0.05$). Thus, the risk of non-healing increases by 4% for each one unit of HADS-A (Table 3).

Discussion

This is the first study to explore the role of depression and anxiety symptoms, before and after amputation surgery, as predictors of the time to achieve clinical results. The results revealed that anxiety symptoms at T0 were independent risk factors for healing in the multivariate model. Although depression symptoms were associated with mortality in the univariate models, in the multivariate analysis they were not shown to be significant predictors. Neither anxiety nor depression symptoms were significant predictors of reamputation. Interestingly, the period when emotional symptoms the greatest impact on clinical outcomes was in the pre-surgery period and not in post-surgery, as originally hypothesized.

Findings showed that the 10-months mortality rate was 9.4%, the reamputation rate was 27.5% and the healing rate was 61.7%. Differences in design, settings, patient selection, patient characteristics, events definitions, follow-up moments and other confounding factors (Apelqvist et al., 2011) hinder a straight comparison of our current findings with the existing literature. Also, this study had a 10-months follow-up, and, for this reason, the authors chose to compare the mortality rate with studies reporting a 1-year follow-up, safeguarding a two-month gap. Thus, observing studies with similar follow-up after LEA, higher mortality rates were found, ranging from 17% to 46% (Fortington et al., 2013; Icks et al., 2011; Ploeg et al., 2005). In two previous Portuguese studies, the mortality rate in diabetic patients with the first DFU at 30 days was 7%, at 90 days it was 17% (Rolim et al., 2015) and at 5-year was 45.6% (95% CI, 39.3–51.8) (Garrido et al., 2016).

Regarding the predictors of mortality, the findings revealed that, although the symptoms of depression in the preoperative period proved to be significant predictors of mortality in the univariate model, when the model was adjusted for the four longitudinal assessments of depression symptoms (T0, T1, T2 and T3), and after controlling for sex, age, ability to walk, duration of diabetes, type of foot, previous and index amputation level and number of complications, depression symptoms were no longer associated with mortality, suggesting the existence of a potential indirect effect of depression symptoms on mortality. Several studies have focused on depression as a predictor of mortality in patients with DM, in patients with a history of ulcers and in patients with the first ulcer, being considered a risk factor for ulceration, but also for delayed healing (Al-Smadi & Gharaibeh, 2019; Ismail et al., 2007; Iversen et al., 2009; Katon et al., 2005; Nowakowska et al., 2019; Shrestha et al., 2019; Vas & Papanas, 2020; Vedhara et al., 2010; Winkley et al., 2012). However, in the only study the authors are aware of which addressed the symptoms of depression as a predictor of mortality after a LEA (addressing amputation from all causes), found no significant relationship between depression and mortality (Singh & Prasad, 2016). In the study of Singh and Prasad (2016), diabetes and the absence of prosthesis-fitting were the only independent predictors of mortality, after controlling for age, gender, level of amputation, social isolation, significant medical co-morbidity (except diabetes) and the presence of mood disorders. Besides, the relationship between depression and diabetes complications appears to be bidirectional (Nouwen et al., 2019). The risk of developing diabetes complications in depressed people is greater than the risk of developing depression in people with diabetes complications, and, in this sample, the level of anxiety symptoms in the pre-surgery was higher than the depression symptoms, which may have influenced results. Future studies, with a larger sample and with a greater number of events, should explore the role of depression symptoms after a LEA as a short- and long-term predictor of mortality. So far, the authors are not aware of other studies that analyzed this relationship. However, it is very important to explore this relationship as half of the patients with DM experience depression symptoms (Jiang et al., 2020).

Concerning reamputation, the rate found in this study was 27.5%, similar to some international studies with a 1-year reamputation rate (Nguyen et al., 2006). For this clinical outcome, the emotional symptoms seem to have no influence and the formulated hypothesis was not confirmed. Although depression is related to the need for initial amputation (O'Neill et al., 2017) and anxiety is identified as a factor responsible for the delay in wound healing in surgical ulcers (Goodwin et al., 2013; Herbert & Cohen, 1993; Walburn et al., 2009), in this study, none of them was a significant predictor. Future studies should explore this relationship allowing the identification of demographic, clinical and psychological determinants of reamputation, as it is highly prevalent.

Few studies have focused on the predictors of healing after a LEA, and the existing literature suggests healing rates ranging between 40% and 57% following a LEA (Nguyen et al., 2006). In our study, 62% of patients healed ten months after a LEA and the higher rate of healing was reached between the first and the sixth month after surgery (53.3%), emphasizing the somewhat long-term care needed for these patients. Regarding healing predictors, anxiety symptoms at T2 and T3 were identified as predictive factors for healing in the univariate model, but in the Cox regression analysis, only anxiety symptoms at baseline (T0) stayed significant predictors. Thus, patients with less than one unit of anxiety symptoms were 4% more likely to heal, therefore, more anxiety was associated with less healing. Interestingly, contrary to our expectations, pre-surgery levels of anxiety had a greater impact on healing than post-surgery levels of anxiety. Previous studies have shown that high levels of stress were associated with delayed healing (in acute and chronic wounds) (Cacha et al., 2019; Gouin & Kiecolt-Glaser, 2011; Guo & DiPietro, 2010), probably as a result of toxic stress, which affects the HPA axis and contributes to inflammation (Downs & Faulkner, 2015), and due to the excessive release of cortisol which is known to delay the onset of the inflammatory phase of the healing process (Vileikyte, 2007). The authors believe this process may be associated with the high level of anxiety symptoms in the pre-surgery period that this sample presented, compared to the levels of anxiety symptoms in the three post-surgery follow-ups. This result reinforces the negative effect of anxiety on the wound healing process and emphasizes the need to provide support and psychological intervention to these patients before surgery.

Although studies suggested the opposite, none of the clinical and demographic variables analyzed to control non-modifiable determinants that could contribute to the clinical results under study were found to be significant (Ploeg et al., 2005). Probably, one of the explanations for this result is the homogeneity and the small sample size of the present study. The sample was characterized by a high prevalence of male individuals with neuro-ischemic foot and a previous history of amputation, in contrast to most previous studies that included more heterogeneous samples regarding demographic and clinical characteristics. This particularity may have significantly underpowered the detection of differences between relevant demographic and clinical characteristics (Thorud, Jupiter, et al., 2016; Thorud, Plemmons, et al., 2016). Future studies should better recognize the regional and national differences in demographic and clinical variables. Therapeutic options and procedures are also different between the two main diabetic foot types and could have been responsible for some of the results and differences found in many publications. As with most of the patients included in previous studies, in the present study, DFU healed more often in neuropathic than in neuroischemic foot mainly because, in the latter type, DFU is more prone to chronicity, infection, tissue destruction and uncontrolled pain, all of which lead to an increased risk of amputation (Katsilambros et al., 2010).

Limitations

This study has some limitations that should be acknowledged, such as a short period of follow-up, a small number of major events, the non-heterogeneity of the sample concerning the extent (size) of the amputation, the homogeneity of sociodemographic characteristics and the inability to control treatment options and surgical procedures. Another important aspect refers to the period in which patients showed emotional symptoms since the assessment of anxiety and depression symptoms was performed between 1 and 48 hours before surgery (T0), during hospitalization, and one month after surgery during follow up consultations (T1). Besides, the reference period in the HADS questionnaire is one week, which does not allow us to understand whether the symptoms were already manifested previously or whether they were a manifestation of pre anxiety/health anxiety. Despite its multicenter characteristics, this study was performed only in diabetes centers from the North of Portugal, which may limit the generalizability of the findings. The small sample size may be responsible for the non-significant results. Therefore, the results should be analyzed cautiously. Futures studies should control for non-modifiable determinants that could contribute to the clinical results under study, such as smoking, chronic obstructive pulmonary disease (or other pulmonary or cardiovascular comorbidities), and renal impairment. Cognitions, social support and pain should also be assessed as determinants and modifiable influencers of clinical outcomes. Future studies should also explore whether the anxiety symptoms affecting the healing process refer to anxiety about the surgery itself or to an underlying anxiety disorder.

Results suggest that approaches to understanding mortality, reamputation and healing, in this population, may be improved through the inclusion of a psychological assessment and a psychological intervention for anxiety symptoms before a LEA surgery. According to Clark and Watson's Tripartite Model (Clark and Watson 1991), differentiating the symptoms of anxiety and depression allows interventions to address the specific and unique symptoms of each construct. Thus, although the data support the beneficial effects of psychological interventions for medically ill patients (White, 2001), there are no studies showing that targeting and intervening in anxiety symptoms can have positive effects on the latter and on clinical outcomes, in patients submitted to a LEA. However, there is evidence that psychological interventions in individuals with diabetes improve glycemic control, depression symptoms and/or diabetes-specific emotional distress (Perrin et al., 2019). Moreover, psychological interventions that address anxiety, such as brief cognitive-behavioral therapy (e.g. relaxation training, induction of imagery through behavioral instructions, promotion of positive coping strategies), is the gold standard intervention and have been widely used in hospitalized patients (Johnston & Vogele, 1993; Spaulding, 2003) as an effective and inexpensive method to reduce health anxiety in patients, in medical settings (Tyrer et al., 2014).

Besides, some studies that have tested stress reduction interventions have shown improved results on wound healing, in surgical wounds (Gouin & Kiecolt-Glaser, 2011) but also in chronic DFUs, increasing the healing rate twofold in the experimental group (87.5% versus 43.8%) when compared to the control group, at three-months follow-up (Rice et al., 2001).

The time segment in which anxiety symptoms have a greater impact on healing, was at baseline, i.e. before surgery. This information is crucial for clinical practice, as it gives insight into when it is the best time for psychological intervention to be delivered, especially when post-surgery measures (T1) have failed to accurately predict mortality, reamputation or healing.

The main strengths of this study included its longitudinal design that identified the psychological predictors of clinical results and the fundamental timeframe for the contribution of each predictor. Also, the sample consisted of hospitalized patients, all indicated for a LEA due to DFU, assessed in face-to-face interviews by a health psychologist, in six major hospitals, 24 hours before surgery (median), unlike most existing studies that assess rates of clinical outcomes by consulting clinical records retrospectively. The interval censorship in healing is also an advantage of this study given that it is difficult (if not impossible) to determine the exact day of healing. The multicenter nature of the research (six centers in the north of the country) is also a positive asset of the present study.

Conclusion

The results highlight the significant contribution of anxiety symptoms in the pre-surgery period to healing after LEA. Symptoms of depression did not prove to be significant predictors. Reamputation and mortality were also not predicted by any of the variables included in the study. However, this study emphasizes the need to provide personalized psychological intervention in order to reduce anxiety during the pre-surgery period and during the post-surgery rehabilitation process.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all participants included in this study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

Al-Smadi, A. M., & Gharaibeh, B. (2019). Prevalence of depression and its associated factors among Jordanian diabetic foot patients. *Health Science Journals*, *8*(3), 43–52.

Apelqvist, J., Elgzyri, T., Larsson, J., Löndahl, M., Nyberg, P., & Thörne, J. (2011). Factors related to outcome of neuroischemic/ischemic foot ulcer in diabetic patients. Journal of Vascular Surgery, *53*(6), 1582–1588. https://doi.org/10.1016/j.jvs.2011.02.006

Bakker, K., Apelqvist, J., Lipsky, B. A., Van Netten, J. J., & Schaper, N. C. (2016). The 2015 IWGDF guidance on the prevention and management of foot problems in diabetes. *International Wound Journal*, *13*(5), 1072. https://doi.org/10.1111/iwj.12496

Boulton, A. J. M., Vileikyte, L., Ragnarson-Tennvall, G., & Apelqvist, J. (2005). The global burden of diabetic foot disease. *Lancet (London, England)*, *366*(9498), 1719–1724. https://doi.org/10.1016/S0140-6736(05)67698-2

Cacha, L. A., Poznanski, R. R., Ariff, T. M., & Latif, A. Z. A. (2019). Psychophysiology of chronic stress: An example of mind-body interaction. NeuroQuantology, *17*(7), 53–63. https://doi.org/10.14704/nq.2019.17.7.2562

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology*, *100*(3), 316–336. https://doi.org/10.1037//0021-843x.100.3.316

Cox, D. R. (2018). *Analysis of survival data*. Routledge.

de Sousa-Uva, M., Antunes, L., Nunes, B., Rodrigues, A. P., Simões, J. A., Ribeiro, R. T., Boavida, J. M., & Matias-Dias, C. (2016). Trends in diabetes incidence from 1992 to 2015 and projections for 2024: A Portuguese General Practitioner's Network study. *Primary Care Diabetes*, *10*(5), 329–333. https://doi.org/10.1016/j.pcd.2016.05.003

Desmond, D., & Gallagher, P. (2008). Coping and psychosocial adjustment to amputation. In P. Gallagher, D. Desmond, and M. MacLachlan (Eds.), *Psychoprosthetics* (pp. 11–21). Springer.

Desmond, D. M., & Maclachlan, M. (2005). The factor structure of the Hospital Anxiety and Depression Scale in older individuals with acquired amputations: A comparison of four models using confirmatory factor analysis. *International Journal of Geriatric Psychiatry*, *20*(4), 344–349. https://doi.org/10.1002/gps.1289

Downs, C. A., & Faulkner, M. S. (2015). Toxic stress, inflammation and symptomatology of chronic complications in diabetes. *World Journal of Diabetes*, *6*(4), 554–565. https://doi.org/10.4239/wjd.v6.i4.554

Fortington, L. V., Geertzen, J. H. B., van Netten, J. J., Postema, K., Rommers, G. M., & Dijkstra, P. U. (2013). Short- and long-term mortality rates after a lower limb amputation. European Journal of Vascular and Endovascular Surgery, *46*(1), 124–131. https://doi.org/10.1016/j.ejvs.2013.03.024

Gallagher, P., Coffey, L., & Desmond, D. M. (2019). Limb loss. In L. A. Brenner, S. A. Reid-Arndt, T. R. Elliott, R. Frank, & B. Caplan (Eds.), *Handbook of rehabilitation psychology* (pp. 257–277). American Psychological Association.

Garrido, S., de Carvalho, A. C., & Carvalho, R. (2016). Long-term prognosis of diabetic patients with a first foot ulcer in a Portuguese Tertiary Care Unit. *Revista Portuguesa de Diabetes*, *11*, 10–13.

Gonzalez, J. S., Vileikyte, L., Ulbrecht, J. S., Rubin, R. R., Garrow, A. P., Delgado, C., Cavanagh, P. R., Boulton, A. J. M., & Peyrot, M. (2010). Depression predicts first but not recurrent diabetic foot ulcers. Diabetologia, *53*(10), 2241–2248. https://doi.org/10.1007/s00125-010-1821-x

Goodwin, R. D., Talley, N. J., Hotopf, M., Cowles, R. A., Galea, S., & Jacobi, F. (2013). A link between physician-diagnosed ulcer and anxiety disorders among adults. *Annals of Epidemiology*, *23*(4), 189–192. https://doi.org/10.1016/j.annepidem.2013.01.003

Gouin, J. P., & Kiecolt-Glaser, J. K. (2011). The impact of psychological stress on wound healing: Methods and mechanisms. *Immunology and Allergy Clinics of North America*, *31*(1), 81–93. https://doi.org/10.1016/j.iac.2010.09.010

Guo, S. A., & DiPietro, L. A. (2010). Factors affecting wound healing. *Journal of Dental Research*, *89*(3), 219–229. https://doi.org/10.1177/0022034509359125

Herbert, T. B., & Cohen, S. (1993). Stress and immunity in humans: A meta-analytic review. *Psychosomatic Medicine*, *55*(4), 364–379. https://doi.org/10.1097/00006842-199307000-00004

Icks, A., Scheer, M., Morbach, S., Genz, J., Haastert, B., Giani, G., Glaeske, G., & Hoffmann, F. (2011). Time-dependent impact of diabetes on mortality in patients after major lower extremity amputation: Survival in a population-based 5-year cohort in Germany. *Diabetes Care*, *34*(6), 1350–1354. https://doi.org/10.2337/dc10-2341

International Diabetes Federation. (2017). *IDF diabetes atlas* (8th ed.). International Diabetes Federation.

Ismail, K., Winkley, K., Stahl, D., Chalder, T., & Edmonds, M. (2007). A cohort study of people with diabetes and their first foot ulcer: The role of depression on mortality. *Diabetes Care*, *30*(6), 1473–1479. https://doi.org/10.2337/dc06-2313

Iversen, M. M., Tell, G. S., Riise, T., Hanestad, B. R., Østbye, T., Graue, M., & Midthjell, K. (2009). History of foot ulcer increases mortality among individuals with diabetes: Ten-year follow-up of the Nord-Trøndelag Health Study, Norway. *Diabetes Care*, *32*(12), 2193–2199. https://doi.org/10.2337/dc09-0651

Jiang, F. H., Liu, X. M., & Yu, H. R. (2020). The incidence of depression in patients with diabetic foot ulcers: A systematic review and meta-analysis. The International Journal of Lower Extremity Wounds, *11*. https://doi.org/10.1177/1534734620929892

Johnston, M., & Vogele, C. (1993). Benefits of psychological preparation for surgery: A meta-analysis. *Annals of Behavioral Medicine*, *15*, 245–256. https://doi.org/10.1093/abm/15.4.245

Jupiter, D. C., Thorud, J. C., Buckley, C. J., & Shibuya, N. (2016). The impact of foot ulceration and amputation on mortality in diabetic patients. I: From ulceration to death, a systematic review. *International Wound Journal*, *13*(5), 892–903. https://doi.org/10.1111/iwj.12404

Kaplan, E. L., & Meier, P. (1958). Nonparametric estimation from incomplete observations. Journal of the American Statistical Association, *53*(282), 457–481. https://doi.org/10.1080/01621459.1958.10501452

Katon, W. J., Rutter, C., Simon, G., Lin, E. H. B., Ludman, E., Ciechanowski, P., Kinder, L., Young, B., & Von Korff, M. (2005). The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care*, *28*(11), 2668–2672. https://doi.org/10.2337/diacare.28.11.2668

Katsilambros, N., Dounis, E., & Makrilakis, K. (2010). *Atlas of the diabetic foot 2*. Wiley-Blackwell.

López-de-Andrés, A., Jiménez-García, R., Esteban-Vasallo, M. D., Hernández-Barrera, V., Aragon-Sánchez, J., Jiménez-Trujillo, I., de Miguel-Diez, J., Palomar-Gallego, M. A., Romero-Maroto, M., & Perez-Farinos, N. (2019). Time trends in the incidence of long-term mortality in T2DM patients who have undergone a lower extremity amputation. Results of a descriptive and retrospective cohort study. *Journal of Clinical Medicine*, *8*(10), 1597. https://doi.org/10.3390/jcm8101597

Monteiro-Soares, M., Martins-Mendes, D., Vaz-Carneiro, A., & Dinis-Ribeiro, M. (2015). Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: A systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews*, *31*(5), 515–622. https://doi.org/10.1002/dmrr.2535

Moxey, P. W., Gogalniceanu, P., Hinchliffe, R. J., Loftus, I. M., Jones, K. J., Thompson, M. M., & Holt, P. J. (2011). Lower extremity amputations-a review of global variability in incidence. *Diabetic Medicine*, *28*(10), 1144–1153. https://doi.org/10.1111/j.1464-5491.2011.03279.x

Nguyen, T. H., Gordon, I. L., Whalen, D., & Wilson, S. E. (2006). Transmetatarsal amputation: Predictors of healing. The American Surgeon, *72*(10), 973–977. https://doi.org/10.1177/000313480607201030

Nouwen, A., Adriaanse, M. C., van Dam, K., Iversen, M. M., Viechtbauer, W., Peyrot, M., Caramlau, I., Kokoszka, A., Kanc, K., de Groot, M., Nefs, G., & Pouwer, F. (2019). Longitudinal associations between depression and diabetes complications: A systematic review and meta-analysis. *Diabetic Medicine*, *36*(12), 1562–1572. https://doi.org/10.1111/dme.14054

Nowakowska, M., Zghebi, S. S., Ashcroft, D. M., Buchan, I., Chew-Graham, C., Holt, T., Mallen, C., Van Marwijk, H., Peek, N., Perera-Salazar, R., Reeves, D., Rutter, M. K., Weng, S. F., Qureshi, N., Mamas, M. A., & Kontopantelis, E. (2019). The comorbidity burden of type 2 diabetes mellitus: Patterns, clusters and predictions from a large English primary care cohort. *BMC Medicine*, *17*(1), 145. https://doi.org/10.1186/s12916-019-1373-y

O'Neill, S. M., Kabir, Z., McNamara, G., & Buckley, C. M. (2017). Comorbid depression and risk of lower extremity amputation in people with diabetes: Systematic review and meta-analysis. *BMJ Open Diabetes Research & Care*, *5*(1), e000366. https://doi.org/10.1136/bmjdrc-2016-000366

OECD/European Observatory on Health Systems and Policies. (2017). *Portugal: Country Health Profile 2017, State of Health in the EU*. OECD Publishing; European Observatory on Health Systems and Policies.

[OECD] Organisation for Economic Cooperation and Development/European Union (EU). (2016). *Health at a glance: Europe 2016 – State of health in the EU cycle. Chapter 3: Diabetes prevalence*. OECD Publishing.

Pais-Ribeiro, J., Silva, I., Ferreira, T., Martins, A., Meneses, R., & Baltar, M. (2007). Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. *Psychology, Health & Medicine*, *12*(2), 225–237. https://doi.org/10.1080/13548500500524088

Pan, W. (1999). Extending the iterative convex minorant algorithm to the Cox model for interval-censored data. *Journal of Computational and Graphical Statistics*, *8*, 109–120. https://doi.org/10.2307/1390923

Pereira, M. G., Pereira, D., & Pedras, S. (2019). PTSD, psychological morbidity and marital dissatisfaction in colonial war veterans. *Journal of Mental Health*, *29*(1), 1–8. https://doi.org/10.1080/09638237.2018.1487532

Perrin, N., Bodicoat, D. H., Davies, M. J., Robertson, N., Snoek, F. J., & Khunti, K. (2019). Effectiveness of psychoeducational interventions for the treatment of diabetes-specific emotional distress and glycaemic control in people with type 2 diabetes: A systematic review and meta-analysis. *Primary Care Diabetes*, *13*(6), 556–567. https://doi.org/10.1016/j.pcd.2019.04.001

Ploeg, A. J., Lardenoye, J.-W., Vrancken Peeters, M.-P. F. M., & Breslau, P. J. (2005). Contemporary series of morbidity and mortality after lower limb amputation. *European Journal of Vascular and Endovascular Surgery*, *29*(6), 633–637. https://doi.org/10.1016/j.ejvs.2005.02.014

Portuguese Diabetes Observatory. (2015). *Diabetes: Facts and numbers 2014: Annual report from Portuguese Diabetes Society*. http://spd.pt/images/ond_2015.pdf

Rice, B., Kalker, A. J., Schindler, J. V., & Dixon, R. M. (2001). Effect of biofeedback-assisted relaxation training on foot ulcer healing. *Journal of the American Podiatric Medical Association*, *91*(3), 132–141. https://doi.org/10.7547/87507315-91-3-132

Robinson, H., Norton, S., Jarrett, P., & Broadbent, E. (2017). The effects of psychological interventions on wound healing: A systematic review of randomized trials. *British Journal of Health Psychology*, *22*(4), 805–835. https://doi.org/10.1111/bjhp.12257

Rolim, D., Sampaio, S., Gonçalves-Dias, P., Almeida, P., Almeida-Lopes, J., & Teixeira, J. F. (2015). Mortalidade depois da amputação. Angiologia e Cirurgia Vascular, *11*(3), 166–170. https://doi.org/10.1016/j.ancv.2015.06.001

Shrestha, M., Al-Ghareeb, A., Alenazi, F., & Gray, R. (2019). Association between subthreshold depression and self-care behaviour in people with type 2 diabetes: A protocol for systematic review of observational studies. *Systematic Reviews*, *8*(1), 167. https://doi.org/10.1186/s13643-019-1084-7

Singh, R. K., & Prasad, G. (2016). Long-term mortality after lower-limb amputation. *Prosthetics and Orthotics International*, *40*(5), 545–551. https://doi.org/10.1177/0309364615596067

Spaulding, N. J. (2003). Reducing anxiety by pre-operative education: Make the future familiar. *Occupational Therapy International*, *10*, 278–293. https://doi.org/10.1002/oti.191

Thorud, J. C., Jupiter, D. C., Lorenzana, J., Nguyen, T. T., & Shibuya, N. (2016). Reoperation and reamputation after transmetatarsal amputation: A systematic review and meta-analysis. *The Journal of Foot and Ankle Surgery*, *55*(5), 1007–1012. https://doi.org/10.1053/j.jfas.2016.05.011

Thorud, J. C., Plemmons, B., Buckley, C. J., Shibuya, N., & Jupiter, D. C. (2016). Mortality after nontraumatic major amputation among patients with diabetes and peripheral vascular disease: A systematic review. *The Journal of Foot and Ankle Surgery*, *55*(3), 591–599. https://doi.org/10.1053/j.jfas.2016.01.012

Tyrer, P., Cooper, S., Salkovskis, P., Tyrer, H., Crawford, M., Byford, S., Dupont, S., Finnis, S., Green, J., McLaren, E., Murphy, D., Reid, S., Smith, G., Wang, D., Warwick, H., Petkova, H., & Barrett, B. (2014). Clinical and cost-effectiveness of cognitive behaviour therapy for health anxiety in medical patients: A multicentre randomized controlled trial. *The Lancet*, *383*(9913), 219–225. https://doi.org/10.1016/S0140-6736(13)61905-4

Vas, P. R., & Papanas, N. (2020). Depression and diabetic peripheral neuropathy: Birds of a feather, but when do they flock together? *Experimental and Clinical Endocrinology & Diabetes*, *128*(5), 347–349. https://doi.org/10.1055/a-0808-4269

Vedhara, K., Miles, J. N. V., Wetherell, M. A., Dawe, K., Searle, A., Tallon, D., Cullum, N., Day, A., Dayan, C., Drake, N., Price, P., Tarlton, J., Weinman, J., & Campbell, R. (2010). Coping style and depression influence the healing of diabetic foot ulcers: Observational and mechanistic evidence. Diabetologia, *53*(8), 1590–1598. https://doi.org/10.1007/s00125-010-1743-7

Vileikyte, L. (2007). Stress and wound healing. *Clinics in Dermatology*, *25*(1), 49–55. https://doi.org/10.1016/j.clindermatol.2006.09.005

Walburn, J., Vedhara, K., Hankins, M., Rixon, L., & Weinman, J. (2009). Psychological stress and wound healing in humans: A systematic review and meta-analysis. Journal of Psychosomatic Research, *67*(3), 253–271. https://doi.org/10.1016/j.jpsychores.2009.04.002

White, C. A. (2001). Cognitive behavioral principles in managing chronic disease. *The Western Journal of Medicine*, *175*(5), 338–342. https://doi.org/10.1136/ewjm.175.5.338

Winkley, K., Sallis, H., Kariyawasam, D., Leelarathna, L. H., Chalder, T., Edmonds, M. E., Stahl, D., & Ismail, K. (2012). Five-year follow-up of a cohort of people with their first diabetic foot ulcer: The persistent effect of depression on mortality. Diabetologia, *55*(2), 303–310. https://doi.org/10.1007/s00125-011-2359-2

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x