Illness Beliefs Predict Mortality in Patients with Diabetic Foot Ulcers

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Structured Abstract

Background: Patients' illness beliefs have been associated with glycaemic control in diabetes and survival in other conditions.

Objective: We examined whether illness beliefs independently predicted survival in patients with diabetes and foot ulceration.

Methods: Patients (n=169) were recruited between 2002 and 2007. Data on illness beliefs were collected at baseline. Data on survival were extracted and used to calculate number of days survived from date of recruitment to the census point (1st November 2011).

Results: Logistic regressions revealed that mortality was predicted by ischemia and illness beliefs, specifically beliefs regarding symptoms (identity beliefs): patients with less ischemia and who believed their foot ulcer was associated with greater symptoms were more likely to die. Cox regressions examined the predictors of time to death and again identified ischemia and identity beliefs as significant predictors of time to death.

Conclusions: These data indicate that illness beliefs have a significant independent effect on survival in patients with diabetes and foot ulceration.

Keywords: illness beliefs; mortality; diabetes; diabetic foot ulcers; self-regulatory model

INTRODUCTION

The psychological functioning of patients with diabetes has been shown to be of clinical importance. For example, indices of psychological functioning have been associated with poorer metabolic control(1); greater treatment non-adherence(2) and an increased risk of diabetic complications.(3) Research with patients with diabetic foot ulcers has also been suggestive of a role for psychological factors in predicting clinical outcomes. For example, in patients with, or at risk, from foot ulceration, depression has been associated with an increased risk of ulceration,(4) delays in the rate of ulcer healing(5) and a 2 fold greater risk of mortality.(6)

The evidence regarding the relationship between psychological functioning and outcomes in patients with foot ulcers has, however, largely focussed on depression and remains equivocal. For example, contrary to the studies cited above, data also exist to suggest that depression is not related to ulcer recurrence(4, 6) or amputation.(7) Similarly, the effect of depression on ulcer healing has been shown not to withstand adjustment for clinical predictors.(8) These observations lead us to speculate that a focus on depression alone may be limiting our understanding of the ways in which psychological functioning can influence clinical outcomes in diabetic foot ulceration; and that it may be necessary to examine the role of other psychological processes.(5, 9)

If we are to extend our assessment of psychological factors beyond depression, which factors are worthy of further enquiry? The influential self-regulatory model of illness(10) can inform this question. The model asserts that patients form illness beliefs when contending with a health threat and that these beliefs play a central role in determining patients' emotional and behavioural responses to their illness. In this way, illness beliefs are 'upstream' from emotional responses, such as depression, to illness. A recent systematic review provides evidence in support of illness beliefs being associated with glycaemic control in diabetes.(11) Furthermore, a study comparing the effects of depression versus illness beliefs in predicting dietary, quality of life and glycaemic control outcomes in diabetes, showed that illness

beliefs were more consistent and stronger determinants of these outcomes than depression.(12) Of particular relevance, however, is recent work with patients with other patient groups which has shown that illness beliefs predict mortality. For example, van Dijk and colleagues(13) reported in a cohort of patients with end stage renal disease that beliefs regarding treatment control predicted mortality: with death being more likely in patients who believed their treatment to be less effective. Similar findings were subsequently reported by Chilcot, Wellstead and Farrington (2011) who also found negative beliefs about the effectiveness of treatment predicted mortality in patients with end stage renal disease.(14) More recently, Crawshaw, Rimington, Weinman and Chilcot (2015) reported that changes in illness perceptions, specifically a change from positive to negative beliefs, predicted mortality in patients who had undergone cardiac vale replacement.(15)

Taken together, the evidence suggests that illness beliefs may predict clinical outcomes, including mortality, in patients with diabetes including those with diabetic foot ulcers. We report on findings from a prospective cohort study in which we examined the effects of illness beliefs on mortality in patients with active ulceration. In line with previous research we hypothesised that the risk of death would be greater in patients with negative beliefs. Our predictive models were constructed to examine whether illness beliefs predicted mortality after examining the role of potential demographic and clinical determinants, as well as depression and coping. Depression was included in view of its prominence in the literature as a determinant of mortality in diabetes.(6, 7, 16) Confrontational coping was also considered a plausible determinant in light of evidence that ulcer history predicts mortality in patients with diabetic foot ulcers(16) and earlier work with this cohort has shown that confrontational coping predicts ulcer healing.(5)

RESEARCH DESIGN AND METHODS

Patients

A convenience sample of patients with diabetes mellitus and a foot ulcer was recruited from outpatient podiatry clinics in secondary care in the UK between January 2002 and January 2007. Patients were recruited into a longitudinal research programme examining psychological and behavioural aspects of diabetic foot ulceration. This study was approved by the North Somerset & South Bristol Research Ethics Committee and all participating patients provided written informed consent.

All clinics subscribed to a standard regimen of foot care, i.e., aggressive debridement at each visit, treatment of infections with antibiotics and the use of removable Scotch-casts and other footwear/devices for offloading ulcers on weight-bearing areas, minimising the likelihood of between-centre variations in treatment outcomes. Inclusion/exclusion criteria ensured the population consisted of patients with neuropathic or neuroischaemic ulcers. Patients were not eligible if they had: no palpable pulses on the affected foot; a history of major amputation (i.e., any lower limb amputation greater than a single digit); known large vessel peripheral vascular disease (e.g., previous bypass surgery, angioplasty); advanced diabetic retinopathy with severe visual impairment; advanced nephropathy (e.g., on dialysis); other severe disabling medical conditions (e.g., stroke); or were being treated with platelet-derived growth factor, tissue engineered skin or total contact casts.

One hundred and sixty-nine patients were recruited. In November 2011, survival data (i.e., deceased versus alive at 1/11/11; and, if deceased, date of death) were requested from General Practitioners. Data were available for 160 patients (n=104 alive at census point; n=32 deceased and date of death known; n=24 deceased and date of death not known). No data were available for 9 patients. These patients were excluded from the analyses. Analyses were conducted to compare patients with and without survival data on all the predictor variables. No differences were evident between the groups on any variable (data not shown), with the exception of age which approached significance (p=0.056): patients with missing survival data were older (mean=65 years) compared with patients with complete data (mean=60 years).

Measures

Illness beliefs: Participants completed the Brief Illness Perceptions Questionnaire (BIPQ)(17) derived from the self-regulatory model of illness.(10) This instrument is recommended in studies involving older participants and/or ill participants and so was selected for the present study. The instrument captured patients' beliefs regarding their foot ulcer in the following domains: identity ('How much do you experience symptoms?'); consequences ('How much does your ulcer affect your life?'); timeline (How long do you think your ulcer will continue?); personal control ('How much control do you feel you have over your ulcer?'); treatment control ('How much do you think your treatment can help your ulcer?'); coherence ('How well do you feel you understand your ulcer?') and emotional response ('How much does your ulcer affect you emotionally?'). The range of scores for each subscale was 0-10, with higher scores indicating a stronger belief in the relevant domain. The reliability, concurrent and predictive validity of the instrument has been reported elsewhere.(17, 18)

Depression: Depression was measured using the depression subscale of the Hospital Anxiety and Depression Scale (HADS).(19) The range of scores for this subscale was 0-21, with higher scores reflecting higher levels of depression. The Cronbach's alpha reliability coefficient for the subscale in the present study was 0.849.

Confrontational coping: Confrontation coping was measured using the confrontation subscale of the Medical Coping Modes Questionnaire.(20) Range of scores for this subscale was 1-26, with higher scores indicating a greater propensity towards confrontational coping. Confrontational styles are characterised as being more controlling, competitive and extroverted. The Cronbach's alpha reliability coefficient for the subscale in the present study was 0.709.

Glucose control: Glycated haemoglobin (HbA1c) was measured to provide a surrogate marker of disease control 2-3 months prior to study entry. HbA1c was measured by cation exchange high performance liquid chromatography using a Menarini HA-8140 analyser and associated reagents (A. Menarini Diagnostics, Wokingham, UK). The assay was maintained in alignment with the Diabetes

Control and Complications Trial method,(21) with no significant assay drift and a between-batch imprecision (CV) of 1.8% (at mean HbA1c 5.5% [37 mmol/mol]). All assays were performed on the same instrument.

Neuropathy and ischaemia assessments: Neuropathy was assessed by applying a 10g nylon monofilament to a number of sites on the affected foot and patients reporting the presence/absence of sensation. Level of neuropathy was based upon the number of tested sites with sensory loss. Percentage rather than absolute values were used as the number of sites assessed varied between podiatrists. Ischaemia was assessed by measuring number of palpable pulses at the dorsalis pedis and posterior tibial areas of the affected foot. All assessments were conducted by the treating podiatrist at each centre.

Ulcer assessments: Data were collected from clinical records on all patients regarding the number of previous ulcers the size of the presenting ulcer and the presence/absence of infection in the presenting ulcer. The assessment of ulcer size involved placing a disposable transparent film over the ulcer and tracing the topical area of the ulcer. The tracing was then placed on a digital tablet (Visitrack: Smith and Nephew, London, UK) and the area of the ulcer was re-traced with a stylus to produce a measurement of absolute ulcer area (in mm^2). These assessments were conducted by the treating podiatrist at each centre.

Statistical methods

One way analysis of variance and chi-square analysis were conducted to compare patients with and without missing survival data on all predictor variables. After checking that assumptions were satisfied, survival analysis was undertaken using both logistic regression (to examine the predictors of whether or not patients died over the observation period) and Cox regression models (to examine the predictors of time to death). For the latter the survival outcome was number of days survived from the date of recruitment to the census point (1/11/11) or death from any cause. Both survival analyses involved two stages. In the first, all potential clinical and demographic predictors and the measures of depression and

coping were examined in univariate analyses to identify significant predictors. In the second step, all seven belief measures were added to only those covariates identified as being significant in the first step. Although this resulted in our models having up to ten predictors, this approach is in keeping with contexts in which it is appropriate to relax the rule of ten predictors per number of outcomes(22); and the self-regulatory model(10) which argues that a patients' understanding of their illness, and subsequent behavioural and emotional responses, are influenced by all of the belief domains represented in the model.

As both the predictor and outcome variables contained missing values, imputation methods were used to maximise the available data for the survival analysis. The independent variables appeared to be missing completely at random: Little's test(23) returned a p-value of 0.74. As only 79 out of the 160 patients contained no missing values, we imputed the missing predictor values using k-nearest neighbours, with k=5, to ensure there was sufficient power.(24) For the outcome measures, survival status was known for 160 patients. Of these, 24 were known to have died, but their date of death was unknown. Thus, we performed multiple imputations to estimate the survival time for these patients. Five imputation techniques were used, the first considered the patients to survive midway between their inclusion into the study and study end date. The second identified the average proportion of time between patients' start dates and the study end date for all the patients who died with a known date of death and estimated the patient's death to be the same ratio between their start date and the study end date. The third imputed survival time was based on the survival time of the patient with the closest start date and the fourth survival time was based on the survival time of the four patients with the closest start date. The fifth survival time was based on the average of the previous four survival times.

Using these datasets we then performed the logistic regression and Cox survival analysis. As the logistic regression does not rely on survival time, we performed the logistic regression without survival imputation. The Cox survival analysis was performed using all five predicted survivals.

Missing imputation methods were implemented using R, a free software environment for computing and graphics.(25) All other analyses used SPSS, Version 19.

Procedure

Patients participated in a prospective observational study. At baseline, the following clinical and demographic data were collected on all participants: age, gender, glycosylated haemoglobin (HbA1c), number of previous ulcers, presence/absence of infection in ulcer, diabetes type, neuropathy and ischemia and ulcer size. Participants also completed self-report measures of illness beliefs,(17) depression(19) and confrontation coping(20) at baseline. Data on survival were collected after the survival census point (1st November 2011).

RESULTS

Cohort Characteristics

Table 1 shows that the average period patients survived in this study was 6 years (range 57-3534 days); the average age of participants was 60 years and, in keeping with the known prevalence of these ulcers, two-thirds of our participants were male. The clinical data indicated moderately high levels of neuropathy and ischemia and average HbA1c levels suggested poor glucose control. Most patients had had an ulcer previously and for approximately one-third of patients the index ulcer was infected at study entry. The psychological data revealed, on average, low levels of depression and modest levels of confrontation coping. The illness beliefs measure indicated that patients reported that they experienced few physical symptoms associated with their ulcers (identity beliefs); believed their ulcers had significant consequences for them (consequence beliefs); and were likely to last a moderately long time (timeline beliefs). Patients also reported moderate levels of personal control over their ulcers (personal control beliefs), but had a greater belief in the effectiveness of treatment (treatment control beliefs).

213 Coherence beliefs suggested that patients' perceived they had a moderately good understanding of their
214 ulcers and also believed that their ulcers affected their emotional well-being.

215 **Table 1: Clinical, demographic and psychological characteristics of the cohort**

	Mean (standard deviation) / Frequency	Available data (N)
Survival (days)	2233 (+/-912)	136
Gender	100 male / 36 female	136
Age	60.25 (+/-11.89)	136
HbA1c % [mmol/mol]	8.70 (+/-1.82); [72 +/-19.9]	129
Number of previous ulcers	1 (+/-3)	120
Ulcer infected at baseline	50 yes / 85 no	135
Diabetes type 1/2	Type 1=39/Type 2=94	133
Ulcer area at baseline (mm^2)	18.02 (34.68)	125
Neuropathy score (%)	72 (+/-33)	130
Ischemia score (%)	73 (+/-34)	131
Depression	5.78 (+/-4.28)	111
Confrontation coping	17.95 (+/-3.7)	109
Identity beliefs	2.99 (+/-2.86)	102
Consequence beliefs	6.53 (+/-2.07)	100
Timeline beliefs	5.97 (+/-1.85)	102
Personal control beliefs	6.03 (+/-2.46)	99
Treatment control beliefs	8.17 (+/-1.36)	101
Coherence beliefs	6.05 (+/-2.15)	102
Emotional response beliefs	5.61 (+/-2.66)	102

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217 **Examining predictors of mortality**

218 The results from univariate logistic regression analyses examining the role of potential clinical and
219 demographic predictors, and depression and coping, on mortality revealed that age (OR 1.035,
220 p=0.022), diabetes type (1/2) (OR .419, p=0.033) and ischemia (OR .975, p <0.0001) were significant
221 independent predictors of whether or not a patient had died by the census point (see Table 2). Neither

depression nor coping emerged as significant predictors. In the multivariate model, the inclusion of the illness belief measures revealed that, although ischemia and diabetes type (1/2) continued to be significant predictors of mortality, age was no longer significant. In addition, coherence beliefs emerged as a significant predictor of mortality (OR .765, p=0.027); and identity beliefs approached significance (OR 1.215, p=0.092). The direction of these associations suggested that patients were more likely to die if they had less ischemia; type 1 diabetes; a poorer understanding of their condition and perceived they had more symptoms. These analyses were repeated following imputation of missing data for the predictor variables, as described above, and the results remained largely unchanged. Specifically, age, diabetes type and ischemia emerged as the only significant predictors in the univariate analysis. The inclusion of illness beliefs in the multivariate model identified only ischemia (OR 0.347 p <0.0001) and identity beliefs (OR 1.871, p=0.054) as significant predictors of mortality. The effects of age and coherence beliefs were reduced to non-significant: p=0.102 and p=0.197 respectively (all other data not shown).

Table 2: Results from logistic regression examining effects of all clinical and demographic covariates and depression and coping (univariate analyses); and only significant covariates from step 1 with illness beliefs (multivariate analysis) on mortality status

Univariate analyses				**Multivariate analysis**			
Covariate	**Odds ratios**	**p**	**95%CI**	**Covariate**	**Odds ratios**	**p**	**95%CI**
Age	1.035	.022	1.005-1.066	Age	1.003	.898	.960-1.048
Gender	1.351	.445	.625-2.922	Diabetes 1/2	0.288	.053	.081-1.018
Ulcer area at baseline (mm^2)	1.001	.893	.990-1.011	Ischemia	0.973	.000	.960-.987
Ulcer infected at baseline	.666	.231	.343-1.295	Consequence beliefs	0.866	.374	.6311-.189
Diabetes 1/2	.419	.033	.189-.931	Timeline beliefs	1.053	.722	.792-1.4
Number of previous ulcers	1.048	.523	.908-1.21	Personal control beliefs	1.137	.233	.921-1.404
HbA1c	.928	.429	.772-1.116	Treatment control beliefs	0.864	.456	.589-1.268
Depression	.946	.232	.864-1.036	Identity beliefs	1.215	.092	.969-1.523
Confrontation coping	1.014	.785	.919-1.118	Coherence beliefs	0.765	.027	.603-.970
Neuropathy	1.011	.072	.999-1.023	Emotional response beliefs	0.879	.234	.710-1.087
Ischemia	.975	.000	0.964-.985				

239 **Examining predictors of time to death**

240 As with the previous analysis, the first step involved univariate Cox regression models in which we
241 examined the role of potential clinical and demographic predictors and depression and coping. The
242 results revealed that only diabetes type (1/2) and ischemia were significant predictors of time to death
243 (see Table 3). In the multivariate model, the measures of illness beliefs were added to these significant
244 covariates. These results showed that ischemia remained a significant predictor of time to death (HR
245 0.976, $p<0.0001$) and that, as with the logistic regression analyses, coherence (HR 0.775, $p=0.036$) and
246 identity beliefs (HR 1.245, $p=0.036$) also emerged as significant predictors, with treatment control
247 beliefs (HR 0.735), $p= 0.086$) approaching significance. Specifically, patients with less ischemia; a
248 poorer understanding of their condition; who perceived they had more symptoms; but also a greater
249 belief in the effectiveness of treatment were most likely to die (see Table 3).

Table 3: Results from Cox regression analyses examining effects of all clinical and demographic covariates and depression and coping (univariate analyses); and only significant covariates from step 1 with illness beliefs (multivariate analysis) on time to death

Univariate analyses				**Multivariate analysis**			
Covariate	**Hazard ratios**	**p**	**95%CI**	**Covariate**	**Hazard ratios**	**p**	**95%CI**
Age	1.021	.179	.990-1.053	Diabetes 1/2	.395	.107	.128-1.223
Gender	1.029	.945	.462-2.291	Ischemia score	.976	.000	.965-.987
Ulcer area at baseline (mm^2)	1.003	.585	.993-1.012	Consequence beliefs	.959	.817	.671-1.370
Ulcer infected at baseline	.792	.512	.394-1.592	Timeline beliefs	.993	.965	.717-1.374
Diabetes 1/2	.304	.026	.107-.868	Personal control beliefs	1.085	.465	.872-1.351
Number of previous ulcers	1.086	.182	.962-1.227	Treatment control beliefs	.735	.086	.517-1.045
HbA1c	.869	.181	.708-1.067	Identity beliefs	1.245	.036	1.014-1.529
Depression	.975	.579	.892-1.066	Coherence beliefs	.775	.036	.610-.983
Confrontation coping	1.014	.782	.918-1.120	Emotional response beliefs	.890	.274	.722-1.097
Neuropathy	1.005	.381	.994-1.017				
Ischemia score	.975	<.0001	.966-.985				

These analyses were repeated following imputation of missing predictor and outcome data as described above, and the results remained largely unchanged. In particular, regardless of which of the 5 imputation methods were used on the time to death variable, the univariate analyses revealed that only the measures of ischemia, diabetes type (1/2) and age were significant independent predictors of time to death (data not shown). Similarly, the multivariate analyses which included the illness belief measures revealed that for all 5 imputation methods, only ischemia and identity beliefs were significant predictors (see Table 4).

Table 4: Cox regression analyses using imputed data to examine effects of significant clinical and demographic and illness beliefs on time to death

	Imputation 1			Imputation 2			Imputation 3			Imputation 4			Imputation 5		
Covariate	**HR**	**p**	**95%CI**	**HR**	**p**	**95%CI**	**HR**	**p**	**95%CI**	**HR**	**p**	**95%CI**	**HR**	**p**	**95%CI**
Age	1.283	.094	.958-1.717	1.315	.065	.983-1.760	1.257	.126	.938-1.684	1.252	.130	.936-1.676	1.272	.108	.949-1.705
Diabetes 1/2	1.661	.192	.775-3.561	1.691	.175	.792-3.609	1.631	.211	.758-3.509	1.715	.173	.790-3.721	1.647	.203	.764-3.552
Ischemia	.425	.000	.313-.578	.420	.000	.308-.573	.418	.000	.308-.566	.405	.000	.298-.551	.415	.000	.305-.564
Consequence beliefs	.732	.176	.465-1.151	.706	.133	.448-1.112	.848	.466	.545-1.32	.828	.407	.530-1.293	.807	.342	.518-1.257
Timeline beliefs	1.280	.236	.851-1.925	1.250	.279	.834-1.873	1.189	.381	.808-1.75	1.157	.460	.786-1.702	1.24	.286	.835-1.841
Personal control beliefs	1.277	.261	.834-1.954	1.276	.264	.833-1.954	1.206	.367	.803-1.812	1.182	.415	.791-1.766	1.228	.333	.810-1.860
Treatment control beliefs	.770	.145	.542-1.094	.746	.101	.526-1.059	.790	.186	.557-1.121	.799	.209	.563-1.134	.783	.173	.550-1.113

Identity beliefs	1.809	.017	1.113-2.940	1.995	.007	1.213-3.281	1.622	.05	1.001-2.628	1.654	.040	1.022-2.675	1.669	.038	1.028-2.71
Coherence beliefs	.796	.227	.550-1.152	.769	.161	.532-1.111	.828	.317	.573-1.198	.796	.220	.552-1.146	.808	.260	.557-1.172
Emotional response beliefs	.729	.120	.489-1.086	.733	.129	.491-1.095	.756	.156	.514-1.113	.737	.128	.497-1.092	.741	.134	.5-1.097

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CONCLUSIONS

We examined the role of illness beliefs in predicting mortality and time to death in patients with diabetic foot ulcers; controlling for other potential clinical and demographic determinants, as well as depression and confrontational coping. These analyses were conducted with and without imputation of missing data. The results from the multivariate models, without imputation, revealed that ischemia, coherence and identity beliefs predicted both mortality and time to death. Specifically, death was more common and occurred more quickly in individuals with less ischemia, who perceived their ulcers were associated with greater symptoms and had a poorer understanding of their condition. When these analyses were repeated with imputation of missing data for the predictor variables (logistic regressions) and imputation of missing data for both the predictor and outcome variables (Cox regressions), the findings were largely unchanged, with ischemia and identity beliefs emerging as significant predictors of both mortality and time to death in all analyses. In view of the increased power associated with the imputed datasets, the discussion of our findings will focus, primarily, on these results.

Our findings have several implications. First, they add to an existing literature which has shown that patients' illness beliefs can influence clinical outcomes in diabetes (e.g., quality of life, glycaemic control(11, 12)). In the present work, both survival analyses identified an independent role for illness beliefs in predicting survival. These results are also in keeping with findings from other patient groups(14, 15) and a recent systematic review(26) all of which have shown how negative beliefs regarding one's illness is predictive of mortality over periods as short as 1.32 years(14) and as long as 10 years.(26)

Second, these results suggest that approaches to understanding mortality risk in this patient group(27) may be improved through the inclusion of illness beliefs in risk models. Our data showed that, even after controlling for other predictors, illness beliefs predicted survival; and that identity beliefs emerged as being of particular importance. Indeed, evidence suggesting that illness beliefs are not only

modifiable, but that illness belief based interventions can produce significant changes in a range of outcomes (e.g., adherence behaviours, mood, return to work) and across many different diseases, including diabetes (28-31); suggests that the measurement of illness beliefs may not only improve our understanding of the risk factors associated with mortality, but could also be incorporated into interventions to improve survival. Although detailed consideration of the features and mechanisms of such an intervention is beyond the scope of this paper, it could be hypothesised that evidence identifying significant prospective relationships between illness beliefs and glycaemic control(11) and illness beliefs and self-care behaviours(32) suggests that any such intervention could improve survival via these pathways.

A related issue concerns the mechanisms underlying the seemingly central role of identity beliefs in predicting mortality. Identity beliefs are concerned with an individual's perception of the extent to which their condition is symptomatic and are often associated with more favourable outcomes (e.g., better adherence, attendance at cardiac rehabilitation, etc.(33, 34) However, in the present study, the experience of greater symptoms was associated with an increased risk of death. This finding could simply reflect the fact patients with greater symptoms had a greater burden of illness which resulted in the greater risk of mortality. Alternatively, the seemingly counter-intuitive role of identity beliefs in this patient group may be related to the unique nature of their condition. Specifically, our inclusion/exclusion criteria were intended to enable us to recruit patients with ulcers which were primarily neuropathic or neuroischemic. One of the defining features of such ulcers is that they are largely pain-free due to the nerve damage associated with neuropathy. Thus, we hypothesise, that patients with a largely painless condition who have high identity beliefs may have poorer outcomes because they erroneously associate pain and related symptoms with severity. Thus, an absence of pain may lead them to underestimate the seriousness of their ulcers; make them less likely to access appropriate healthcare and this may, in turn, give rise to the poorer mortality outcomes observed in our data.

A further issue relates to our finding that ischemia was associated with a survival advantage. As with identity beliefs, ischemia was found to predict both mortality and time to death in all analyses, thereby suggesting that, although counterintuitive, it was a robust finding. However, a number of issues should be considered when interpreting this result. First, our approach to measuring ischemia involved a single assessment (i.e., the measurement of the number of palpable pulses). However, the accurate measurement of ischemia requires multiple, not single, methods.(35) Thus, our approach, while pragmatic (we selected one method which could be conducted rapidly across all clinics), lacked precision and this may have contributed to our finding. Second, as stated, our inclusion criteria were intended to enable us to recruit patients with neuropathic or neuroischaemic ulcers i.e., patients with no palpable pulses (severe ischemia) were excluded. As a result, the patients in this cohort with the greatest levels of ischemia, were likely to be individuals with only moderate ischemic disease; and patients with low levels of ischemia likely to be patients experiencing greater neuropathy. As the treatments for microvascular complications such as neuropathy are considered not to be as effective as treatments for macrovascular complications,(36) this might explain the apparent survival advantage in our patients with moderate ischemia. In other words, moderate ischemia in this study may have been a marker of less severe neuropathy thus contributing to the observed relationship with mortality and time to death.

The final issue relates to the observation that depression did not influence survival. This finding is consistent with research showing that the effects of depression on clinical outcomes in diabetes are equivocal.(27) Indeed, our data support a growing literature suggesting that a focus on depression in isolation may not be helpful when considering how psychological factors, and psychological interventions, influence clinical outcomes in diabetes.(12, 37, 38) In the case of the present work, we were unable to detect a statistically significant independent effect of depression. However, it is worth noting that post-hoc analyses (data not shown) revealed that depression was significantly positively correlated with identity beliefs, thus suggesting the potential for an indirect effect of depression on mortality outcomes.

In summary, our analyses have shown a significant independent effect of patients' illness beliefs on survival in patients with diabetic foot ulcers. Potential limitations of this work relate to the modest sample size and the exclusion of patients for whom we were unable to obtain survival data from clinical records. However, it is worth noting that our sample size was greater than the mean sample size reported in a systematic review of previous work examining the role of illness beliefs in survival(26); and our excluded patients did not differ from the rest of the cohort on any of the predictors of survival. Finally, our approach to measuring illness beliefs was pragmatic but lacked precision. Although the brief IPQ is particularly suitable for studies with older and/or frail patients, it relies on single items for the measurement of each belief domain and this necessarily precludes a detailed analysis of patients' beliefs. Notwithstanding these limitations, these results broaden our understanding of the role of psychological processes in diabetes and add to the growing literature suggesting that individuals' beliefs about their illness may have prognostic significance.

AUTHOR CONTRIBUTIONS

KV designed the research, secured funding, conducted data analysis and wrote the manuscript. KV is also the guarantor of this manuscript. KD contributed to data collection, analysis and discussion and review of manuscript. JNVM contributed to data analysis and discussion and review of manuscript. MW contributed to data collection, analysis and discussion and review of manuscript. NC contributed to study design and discussion and review of manuscript. CD contributed to study design and discussion and review of manuscript. ND contributed to study design and discussion and review of manuscript. PP contributed to study design and discussion and review of manuscript. JT contributed to study design and discussion and review of manuscript. JW contributed to study design and discussion and review of manuscript. AD contributed to study design and discussion and review of manuscript. RC contributed to study design and discussion and review of manuscript. JR contributed to data analysis and discussion and review of manuscript. DS contributed to data analysis and discussion and review of manuscript.

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