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ORIGINAL ARTICLE

The impact of foot ulceration and amputation on mortality in diabetic patients. I: From ulceration to death, a systematic review

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Abstract

A great deal of emphasis, clinical and financial, is placed on limb salvage efforts in diabetic patients suffering from lower extremity ulceration. This is because of the impression that amputation in such patients may be a proximal cause of death. While amputation is certainly a negative clinical outcome, it is not entirely clear that it causes death.

In this systematic review, we examine the available literature to attempt to understand the role that the ulceration itself may play in mortality. In brief, we searched for human studies in OVID, CINAHL and the COCHRANE CENTRAL DATABASE from 1980 to 2013, looking for articles related to ulcer or wound of the foot, in patients with diabetes or peripheral vascular disease, and death. We looked for articles with 5 years of follow-up, or Kaplan–Meier estimates of 5-year mortality, and excluded reviews and letters. Articles were assessed for quality and potential bias using the Newcastle–Ottawa scale.

We find that while the patient populations studied varied widely in terms of demographics and comorbidities, limiting generalisability, 5-year mortality rates after ulceration were around 40%. Risk factors for death commonly identified were increased age, male gender, peripheral vascular disease and renal disease.

Introduction

An estimated 300 million people worldwide will suffer from diabetes by 2025, and the prevalence of type II diabetes in the USA in 1980 was 6.6% or 8 million (1). The Centers for Disease Control estimated that in 2010, there were 25.8 million adults in the USA, or 8.3% of the adult population, with diabetes. The negative consequences of diabetes are well documented and include retinopathy, nephropathy and eventual dialysis, neuropathy, increased risk of cardiovascular events, and so forth. In terms of lower limbs, the influence of diabetes may lead to macrovascular and microvascular damage, causing

Key Messages

- lower limb ulceration in diabetic patients is associated with amputation and high mortality
- in this systematic review, we quantify the role new-onset ulceration plays in mortality in diabetic patients
- five-year mortality rates after ulceration were around 40%
- risk factors for death commonly identified were increased age, male gender, peripheral vascular disease and renal disease

difficulties in wound healing (2,3). This, combined with neuropathy, can lead to non-healing ulcers (4). This ulceration may precipitate amputation, and, ultimately, in concert with the diabetes-associated peripheral vascular disease (PVD), it may lead to death (5,6). The incidence and prevalence of foot ulcers in diabetic patients are estimated at 2% and 5–7%, respectively (7,8). Among those with ulcers, mortality is roughly double that among diabetic patients without foot ulcer (7,9,10). It has further been noted that up to 85% of diabetes-related lower extremity amputations are preceded by foot ulcers (11,12). More generally, the incidence of amputation has been estimated as being more than 10 times higher in diabetic patients than in non-diabetic patients (13,14).

A widely held belief in the medical communities is that lower extremity amputation in diabetic patients suffering from diabetes-related lower extremity complications is a proximal cause of death. However, it is difficult to determine whether the underlying diseases led to increased mortality alone or if the amputation hastens the process. Limb salvage efforts are already of interest because they may preserve the quality of life, although the evidence on this topic is not definitive (15–17), and minimise the risk of deconditioning (18). Given the concern with mortality after amputation, these efforts are even further emphasised. It is difficult to find direct evidence that amputation leads directly to death, although it is suggested that amputation does have an impact on vascular dynamics (19–21).

Part of the difficulty in assessing the role of amputation in the eventual death after ulceration is closely related to study design. For example, Moulik *et al.* examined patients with new-onset ulcers and followed them up until death or the end of the study period (10). They compared the rates and timing of death between those patients who had amputation and those who did not. For both groups, the time to death was considered as being from onset of ulcer; in particular, in the amputation group, time to death was not the time between amputation and death, but the time between ulceration and death. Thus, even if the time to death was the same in both groups, it is entirely possible that amputation hastened death, and we simply cannot see this as an effect of amputation. This difficulty is not resolved simply by measuring time to death from the signal event, either ulceration or amputation, respectively, in our groups above, because if we do so, we are comparing two distinct populations: those with new-onset ulcer, and their time until death from that ulceration; and those who had an ulceration in the past and now have a new amputation, and their time until death from that amputation.

There appears no simple way out of this conundrum, and no easy way to directly assess the impact of amputation on mortality in those with ulceration secondary to diabetes. Cox regression using amputation status as a time-varying covariate is an attractive option, but there is still information to be gleaned from the published literature, without developing and carrying out new studies. In this article, and a few to follow, we hope to try to address these issues in a stepwise fashion. First, we explore in the current article whether and how ulceration in diabetic patients is associated with death. While we do not have an easy comparator population to examine – we cannot simply compare with diabetic patients without ulceration, as this would involve considering issues such as age or duration of diabetes – we can at least begin to understand mortality rates after ulceration. In the future, we hope to examine the rates and timing of amputation, after new-onset ulceration; as well as timing from amputation to death, both in those with and those without ulceration. This will give a notion of the direct impact of amputation on mortality. Together, we hope to gain a clearer view of the role of amputation in mortality of diabetic patients with lower extremity amputation. Further, we hope that the information garnered will suggest new directions of study to further clarify these issues.

Our particular interest is in outcomes after ulceration. One can ask the following questions: after an initial ulceration, what is the long-term prognosis? How likely are such patients to suffer from further ulcers, amputations or death? We focus here on the last question, and leave the second last question to another paper.

Methods

On 17 August 2013, DJ, JT and NS participated in the following systematic search for manuscripts relating to rates of death after ulceration. We searched OVID, CINAHL and the Cochrane CENTRAL database using the following search terms:

("ulcer*" or "wound*") and ("foot" or "feet" or "lower extremit*") and ("PVD" or "peripheral vascular disease" or "diabet*") and ("death" or "survival" or "mortality").

In making the choices outlined below for inclusion and exclusion, we aimed to keep our review as broad as possible, while excluding both non-human results and lower quality studies. We searched for papers published between 1 January 1980 and 31 August 2013 and required that abstracts were available. No language restrictions were placed on the searches. Searching in OVID was limited to core clinical journals and human-related results. We do not have a review protocol beyond that presented in this section, and the review is not registered.

For filtering the abstracts, and then the full manuscripts when warranted, we used the following criteria. We included only human studies, allowing cohort studies, longitudinal studies, case–control studies, cross-sectional studies and prospective clinical trials. We excluded case series, letters, systematic reviews or meta-analyses (although these were searched for the purpose of obtaining further references), abstracts or studies that included only with traumatic amputation. We required that the follow-up time after initial presentation had a mean of at least 5 years, or that Kaplan–Meier estimates for 5-year survival were presented. Five-year mortality is an outcome of general interest in studying diabetic patients and those suffering other pathologies, and thus seemed an appropriate assessment for our aims. We allowed new-onset ulcer patients, as well as patients with a history of ulceration on study entry as our study group, in order to ensure broad inclusion. As Charcot neuroarthropathy differs in aetiology from that of both osteomyelitis and non-healing ulcers of the foot, we excluded Charcot patients in our review, although studies were not excluded if they included Charcot patients, and some results on Charcot patients were presented, if they were of interest.

Each paper was summarised in paragraph form by either DJ or JT. These reports were then reviewed for accuracy, further summarised, and organised into one of the groups of studies shown in Results section, by DJ. DJ and JT also summarised

the results in Table 2. Final data were reviewed and approved by all the authors. Summaries were to include study year and location; numbers of patients in the study; distribution of patients into study groups, although what the study groups were did vary by study; mean age within study groups; distribution of gender within study groups; mortality rate within study groups; method of mortality rate assessment; distribution of diabetes type within study groups; follow-up times, either mean or median, as dictated by study design, within study groups; ulcer assessment and study inclusion and exclusion criteria; prevalence of PVD, if available, within study groups and any factors identified as associated with mortality, either in the entire study population or within specific study groups. The main outcome measure was 5-year mortality, either exact or as estimated by Kaplan–Meier curves, in diabetic patients with ulcers. Five-year mortality rates in other groups of patients (e.g. diabetic patients without ulcers) were also reported.

The issue of outcome level bias has been discussed in the introduction. Study bias was assessed using the Newcastle–Ottawa scale (22).

Results

We recovered 27 abstracts from Cochrane, none of which were retained for review, based on the examination of abstracts. From OVID, we recovered 122 abstracts and included 17 for closer examination. CINAHL yielded 151 articles, 38 of which were included for closer examination. We decided to look at the full text of 10 of the OVID articles and 14 of the CINAHL articles, although 6 articles were in common to both lists. Upon examination of the 18 full-text articles, we removed 11 from consideration for having either too short follow-up times (less than an average of 5 years) or an inappropriate outcome (no mention of mortality). This left us with seven papers of interest (Carrington, Faglia, Ghanassia, Iversen, Morbach, Sohn and Young) (23–29). Further searching of the references of these papers yielded five more of interest (Table 1) (Gazis, Pinto, van Baal, Winkley and Apelqvist, the last included although it had short follow-up time because it had estimates of 5-year mortality) (30–34).

General quality of the reviewed articles was high, with the exception of the article by Gazis *et al.* As noted elsewhere, and highlighted by our division of studies into groups below, the studies did not examine uniform populations; some studies focused on more seriously ill patients, or patients who had been hospitalised. All studies were cohort studies, often comparing subgroups of the patients within the study. The focus of some studies was Charcot neuroarthropathy, although those studies did also include patients with ulceration and no Charcot. Follow-up quality was usually not an issue, as we specifically chose articles with a suitable follow-up. For a summary of article quality, see Table 2.

General outcomes after ulceration

Carrington et al.

The focus of the study of Carrington *et al.* is whether motor nerve conduction velocity, as part of a neurological examination, can be used to help predict lower extremity–related outcomes in diabetic patients (35). Consecutive patients who presented to a diabetes centre and consented to participate were enrolled in the study in 1994 and 1995, and followed up yearly until 2000. There were 51 diabetic patients without neuropathy, 67 diabetic patients with neuropathy and 34 patients with history of ulcer. No mention was made of whether these patients (with history of ulcer) were neuropathic or not. We excluded from our analysis the non-diabetic and the Charcot patients. The investigators excluded patients with an ankle-brachial index (ABI) <0.75, any patient with an active ulcer and any patient with a history of amputation.

Table 1 Studies included and excluded from our review

Included	Excluded
From literature search:	Jeffcoate (38): follow-up too short
Carrington (35)	Moulik (10): follow-up too short
Faglia (24)	Ndip (39): follow-up too short, abstract only
Iversen (26)	Ramsey (7): follow-up too short
Morbach (27)	Scatena (40): follow-up too short
Young (29)	Ismail (41): follow-up too short
Ghanassia (25)	Coppini (42): no information on rate of death after ulceration, although it is noted that 4.4% of those who died had had ulceration
Sohn (28)	
	Ahroni (43): follow-up too short
From manuscript reading:	Driver (44): no information on rate of death after ulceration
Gazis (30)	Pound (36): follow-up too short
Winkley (33)	Treece (45): follow-up too short
Pinto (31)	
van Baal (32)	
Apelqvist (34)	

The mean age was 56 years and was similar across the three groups. While the diabetic patients with a history of ulceration and those with neuropathy had a male/female ratio of about 2:1, those without neuropathy had roughly the same number of men and women. The average duration of diabetes was roughly 18 years. Six-year mortality rates in patients with diabetes with and without neuropathy and those with a history of ulceration was 16.4% (11), 7.8% (4) and 35.3% (12), respectively. Overall, 6-year mortality in those without ulceration history was 15/118, or 12.7%.

These are not new-onset ulcers, but rather healed ones. In a slightly different approach to the outcomes of ulceration, Pound *et al.* examined ulcer- and amputation-free survival in patients who presented with ulcer that subsequently healed. Ulcer-free survival is viewed as a proxy for repair or control

Table 2 Summary of included studies

Study	Year	Group	*n*	Mean age	Male	Type I DM	Mortality	Follow-up (months)	Mortality assessment	Ulcer	PVD	Setting	Risk factors for death
Winkley *et al.*	2011	Ulcer	253	62 (13.9)	161 (63.6%)	17%	92/253 (36%)	60	Exact 5-year mortality	First ulcer	ABI >0.9: 193 (76.3%), ABI >0.5–0.9: 60 (23.7%)	UK	5-Year mortality associated with age (HR 1.06, 95% CI 1.04–1.08), mean HbA1c (HR 0.86, 95% CI 0.74–1.00), minor depression (HR 1.93, 95% CI 1.00–3.74) and major depression (HR 2.18, CI 95% 1.31–3.65)
Young *et al.*	2008	Ulcer (1995–1999)	404	63.3 (13.8)	62%	30%	48%	60	Exact 5-year mortality	New-onset	Ischaemic ulcer: 52%	1995 and 1999 (before policy change)	Five-year mortality rates were significantly higher in cohort 1 (48%) than in cohort 2 (26.8%). This was also reflected when categorising patients into ischaemic and neuropathic ulceration groups (cohort 1: 58% and 36% versus cohort 2: 36% and 19%, respectively). Furthermore, those patients who died within 5 years in cohort 2 were on average 3.5 years older than those in cohort 1 and average age of death was 70.4 ± 11.8 in cohort 1 and 73.9 ± 10.1 in cohort 2
		Ulcer (2001–2004)	251	61.9 (14.9)	66%	23%	26.80%	60	Exact 5-year mortality	New-onset	Ischaemic ulcer: 48%	2001 and 2004 (after policy change)	
Faglia *et al.*	2001	Ulcer	115	78.3 (15.3)			51/115 (44.3%)	78.3 (15.3)	Crude estimates – proportion of patients who died. All followed up for at least 5 years. KM estimates performed but not available	Admitted to the hospital for foot ulceration	95 (82.6%) had neuropathy 97 (84.3%) had PAD (ABI < 0.9, and 36 [31.3%] patients with ABI < 0.5)	Hospitalised for ulcer	Following multivariate analysis, independent risk factors for death were ABI < 0.5 (HR 2.29, 95% CI 1.29–4.08), age (HR per increase of 1 year was 1.05, 95% CI: 1.02–1.08), and female sex (HR 1.96, 95% 1.08–3.56)

Table 2 Continued

Study	Year	Group	*n*	Mean age	Male	Type I DM	Mortality	Follow-up (months)	Mortality assessment	Ulcer	PVD	Setting	Risk factors for death
Ghanassia *et al.*	2008	Ulcer	89	63.8 (10.8)	62/89 (69.7%)	11/89 (12.4%)	46/89 (51.7%)	79.4 (13.3)	Crude estimates – proportion of patients who died. All followed up for at least 5 years. KM estimates performed but not available	Admitted to the hospital for foot ulceration	75 (84.3%) had ischaemic wounds 15 (16.9%) underwent vascular surgery	Hospitalised for ulcer	Increased age, renal impairment and history of amputation were found to be significant in the univariate analysis but only renal impairment was found to remain significant following multivariate analysis (HR 4.57, 95% CI 1.1–19.4).
Pinto *et al.*	2008	Ulcer	102	66.7 (9.8)	55.80%	0	14/102 (13.7%)	60	Not clear, appears to be exact 5-year mortality.	Hospitalised with ulceration and diabetes but not new vascular event	ABI average: 0.72 (0.2)		Age, duration of diabetes, HbA1c and foot ulceration were significantly associated with cardiovascular morbidity.
		DM only	123	66.9 (13)	67.56%	0	10/123 (8.1%)	60	Not clear, appears to be exact 5-year mortality		ABI average: 0.89 (0.41)		
van Baal *et al.*	2010	Ulcer	109	58.6 (12.5)	73/109 (67%)	32/109 (29.4%)	40%	60	5-year KM estimates	Neuropathic ulcer matched to Charcot group	NR		Age and renal dysfunction were independent predictors of mortality but Charcot and sex were not
Iverson *et al.*	2009	Ulcer	155	67.2 (14)		26%	49%	Up to 120	10-year KM estimates	Ulcer history based on question-naire		HUNT 2	Older age, male sex, lower education, smoking and larger waist circumference were significantly associated with death. Following adjustment for these variables in a Cox regression analysis, individuals with diabetes and a history of ulceration were associated with a an HR of 2.29 (95% CI 1.82–2.88) hazard risk for mortality versus

Table 2 Continued

Study	Year	Group	*n*	Mean age	Male	Type I DM	Mortality	Follow-up (months)	Mortality assessment	Ulcer	PVD	Setting	Risk factors for death
													non-diabetic patients and HR 1.47 (95% CI 1.14–1.89) compared with diabetic patients without a history of ulceration.
		DM only	1339	65.6 (13.6)		16.90%	35.20%	Up to 120	10-year KM estimates			HUNT 2	
Carrington *et al.*	2002	Ulcer	34	55 (49–59)	23/34 (67.6%)	15/34 (44.1%)	12/34 (35.3)	72	Exact 6-year mortality	History of, but no, current ulcer	ABI: 1.17, calcification 8/34 (23.5%)	routine diabetic clinic	Higher creatinine, lower motor nerve conduction velocity, >25 mm Hg $TcPO_2$
		DM with neuropathy	67	58 (48–62)	50/67 (74.6%)	34/67 (50.7%)	11/67 (16.4%)	72	Exact 6-year mortality		ABI: 1.15, calcification 14/67 (20.9%)		
		DM only	51	53 (47-60)	26/51 (51.0%)	25/51 (49.0%)	4/51 (7.8%)	72	Exact 6-year mortality		ABI: 1.15, calcification 4/51 (7.8%)		
Morbach *et al.*	2012	Ulcer	247	68.8 (10.9)	145/247 58.7%	31/247 (12/6)	45.8% (30.2% in those without PVD, 58.8% in those with PVD)	68.4 (52.8)	5-year KM estimates	New-onset ulcer, no amputation history	137/247 (55.5%), ABI < 0.9 with additional ultrasonography or angiography	Single diabetes centre	Age, male gender, CRI, dialysis
Sohn *et al.*	2009	Ulcer	2100	62.8 (9.8)	97.90%	NR (duration >6 years:= 39.8%)	37%	~60 (states 4-5 years)	Unclear. Appear to be crude estimates – proportion of patients who died	Newly diagnosed) based on ICD-9	PVD: 34.5%	VA medical records (ICD 9)	Age, male gender, race, married, heart disease, stroke, pulmonary disease, neurologic disorders, diabetes duration, deficiency anaemias, paralysis, coagulopathy, PVD, CHF, renal failure, cancer, liver disease,

Table 2 Continued

Study	Year	Group	*n*	Mean age	Male	Type I DM	Mortality	Follow-up (months)	Mortality assessment	Ulcer	PVD	Setting	Risk factors for death
		DM only	2100	62.7 (9.6)	97.30%	NR (duration >6 years: = 40.9%)	18.80%	~60 (states 4–5 years)	Unclear. Appear to be crude estimates – proportion of patients who died	Hx based on ICD-9	PVD: 8.7%	VA medical records (ICD 9)	
Gazis *et al.*	2004	Ulcer	47	59.7 (12.6)	26/47 (55.3%)	18/47 (38.3%)	16/47 (34%) at an average of 3.1 ± 2.7	63.6 (46.8)	Crude estimates – proportion of patients who died. All followed up for at least 5 years. KM estimates performed but not available	Uncomplicated neuropathic ulcer	All patients in the ulcer group had at least one palpable pulse	Diabetic clinic	Not formally analysed
Apelqvist *et al.*	1993	Ulcer (healed)	345	63 (17)	182	NR (duration 16 ± 12 years)	42%	60 (6–84, median 48)	KM estimates	Current ulcer at start	Systolic Blood pressure: 156 (24) Systolic ankle pressure: 132 (47) Systolic toe pressure: 83 (43)	Referred to Internal Medicine (1983-1990)	Associated with previous amputation
		Ulcer (amputated)	123	70 (12)	67	NR (duration 17 ± 13 years)	63%	60 (6–84, median 48)	KM estimates	Current ulcer at start	Systolic Blood pressure: 163 (25) Systolic ankle pressure: 90 (44) Systolic toe pressure: 34 (28)	Referred to Internal Medicine (1983–1990)	

DM, diabetes mellitus; KM, Kaplan–Meier; PVD, peripheral vascular disease; VA, Veteran's Affairs.

of the underlying pathology (36). The authors note from their survival analysis that the most rapid rate of recurrence is within the 50 days after healing, and that new ulcerations are unlikely if a patient has remained healed for a year. Given these results of Pound *et al.*, one may ask whether the patients in this study are healthier than those studied in the following studies (36).

Outcomes after new-onset ulcers

Sohn et al.

While the goal of the study by Sohn *et al.* was to compare mortality risks in diabetic patients with Charcot neuroarthropathy with mortality risks in other diabetic patients, their study provides valuable information about mortality in diabetic patients with ulcers (28).

Patients were identified from Veteran's Affairs (VA) system records for the fiscal year 2003, with diabetes being defined as taking prescription diabetes medication or having a diabetes-related hospitalisation or office visit. Patients with newly diagnosed Charcot (as assessed with ICD-9 codes) in 2003 were first selected: there were 1050 such patients. Patients with new-onset ulcers (identified by ICD-9 codes), and diabetic patients without Charcot or new-onset ulcers were propensity score matched to patients with Charcot, in a ratio of 2:1. Propensity score matching included age, race, gender, diabetes duration and diabetes control. Five-year mortality was assessed using VA records. A variety of comorbid conditions were evaluated and included in the Cox proportional hazards model.

The 2100 new-onset ulcer patients comprised 97.9% males, with an average age of 62.8 years. About 39.8% of them had had diabetes for at least 6 years, although 31% had their diabetes well controlled with an average glycosylated haemoglobin of <7 over the previous year. Notably, 38.4%, 34.5%, 14.4% and 11.4% of these patients had ischaemic heart failure, PVD, stroke and renal failure, respectively. Of the diabetic patients without ulcer or Charcot, 18.8% died within the 5-year follow-up, as compared with 37% of those with ulcer. Significant risk factors for death included ulcer, male gender, unmarried status, increased age, liver disease, renal failure, congestive heart failure and PVD. The authors did not independently examine the risk factors for death in the ulcer population.

Long-term outcomes after ulceration

Iversen et al.

In a population-based sub-study from the Nord-Trøndelag Health Study (HUNT 2) conducted from 1995 to 1997, Iversen *et al.* examined the long-term mortality of 63 632 non-diabetic individuals, 1339 diabetic individuals without a history of ulceration and 155 diabetic individuals with a history of ulceration (25). Definitions of ulceration and diabetes were based on a questionnaire (wound requiring >3 weeks to heal). Records were examined via the Norwegian Causes of Death Registry 10 years later in December 2005.

The average age of non-diabetic patients was 49.7 ± 17.3 years, of diabetic patients without ulcerations was 65.6 ± 13.6 years and of diabetic patients with ulceration was 67.2 ± 14 years. Prevalence of type I diabetes was 16.9% among the diabetic patients without ulceration and 26% among those with a history of ulceration. Prevalence of amputations (any amputation from toes to femur) at the beginning of the study was found to be 0.7% in diabetic patients without history of ulceration and 5.2% in those with a history of ulceration. Ten-year mortality was found to be 10.5% among 3632 non-diabetic individuals, 35.2% in 1339 diabetic individuals without a history of ulceration and 49% in 155 diabetic individuals with a history of ulcerations. Older age, male sex, lower education, smoking and larger waist circumference were significantly associated with death. Following adjustment for these variables in a Cox regression analysis, individuals with diabetes and a history of ulceration were associated with a 2.29 (95% CI 1.82–2.88) hazard risk for mortality versus non-diabetic patients and 1.47 (95% CI 1.14–1.89) hazard risk compared with diabetic patients without a history of ulceration.

Morbach et al.

Morbach *et al.* followed up 247 patients with new diabetic foot ulceration without previous major amputation from June 1998 to December 1999 until May 2011 or until death (27). Patients (or relatives or family physicians, if required) were contacted yearly to determine the outcomes. The mean follow-up was 5.7 ± 4.4 (range: 0.003–13.2) years. The mean age was 68.8 ± 10.9 years; 216 (87.5%) had type II diabetes. A total of 213 (86.2%) patients had neuropathy and 137 (55.5%) had PVD at the start of the study. Of the 247 patients, 174 (70.4%) had died by year 10. The overall 5-year mortality rate was 45.8%, 30.2% in patients without PVD and 58.8% in patients with PVD. Major amputation rate was 8.7%, 12.5%, 15.9% and 22.3% at years 1, 3, 5 and 10, respectively. Predictors of mortality according to Cox regression were age, male gender, chronic renal insufficiency, dialysis and PVD.

Young et al.

Adding to the complexity of interpretation of the mortality rate of diabetic patients with ulcerations, Young *et al.* found differences in mortality rates before and after an aggressive cardiovascular risk policy became the standard of practice at the Diabetic Foot Clinic in the Royal Infirmary of Edinburgh in 2001 (29). Survival following new onset of ulceration of two cohorts was recorded using death certificates. Cohort 1 included patients referred between 1995 and 1999 (before policy change) and cohort 2 included patients referred between 2001 and 2004 (after policy change). All the patients were followed up until 2008. A total of 404 patients were followed up in cohort 1 with an average age of 63.3 ± 13.8 years, 62% male, 52% with ischaemic ulcers and 70% with type II diabetes. Cohort 2 consisted of 251 patients with an average age of 62 ± 14.9 years, 66% male, 48% with ischaemic ulcers and 77% with type II diabetes. Five-year mortality rates were significantly higher in cohort 1 (48%) than in cohort 2 (26.8%). This was also reflected when categorising patients into ischaemic and neuropathic ulcerations (cohort 1; 58% and 36%, versus cohort 2; 36% and 19%, respectively). Furthermore, those patients who died within 5 years in cohort 2 were on average 3.5

years older than those in cohort 1, with average age of death 70.4 ± 11.8 years in cohort 1 and 73.9 ± 10.1 years in cohort 2.

Major amputation rate was 11.3% in cohort 1 at the study end date. No significant difference in 5-year mortality was found between those with amputation (47.8%) and those without (48.8%).

Apelqvist et al.

Apelqvist *et al.* examined the following question: after an initial ulceration has healed, what is the likelihood of further ulcers, further amputations or death? (34) There were 345 patients who had healed primarily (healed without amputation) and 123 who had undergone amputation before healing. These patients were followed up after healing for a median of 4 years. The patients who healed after amputation were slightly older, had lower distal perfusion pressure and had higher rates of neuropathy compared with those healed without amputation. There were no differences in terms of gender, diabetes duration or treatment, blood pressure or smoking history. The 1-, 3- and 5-year rates of new ulceration were 34%, 61% and 70%, respectively. The authors noted that the ulceration rates were slightly higher in those with a history of previous amputation. Amputation rates at 1, 2 and 3 years were 6%, 16% and 22%, respectively. Survival rates at 1, 3 and 5 years were 80%, 59% and 27%, respectively, in those with previous amputation and 92%, 73% and 58%, respectively, in those whose ulcers primarily healed. They noted that these mortality rates are roughly four and two times as high as those in an age- and gender-matched sample from the entire Swedish population, respectively.

Outcomes in sicker patients

Faglia et al.

Faglia *et al.* followed up 115 subjects admitted to the hospital for foot ulceration between 1990 and 1993 until 1998. The mean follow-up was 78.3 ± 15.3 months (range 60–106) (24). At the start of the study, 95 (82.6%) patients had neuropathy and 97 (84.3%) had PVD [ABI < 0.9 and 36 (31.3%) patients with ABI < 0.5]. The average age was 63 ± 9.9 years and 84 (73%) were males. Twenty-nine (29.9%) patients underwent vascular interventions on the lower extremities. Death occurred in 51 of 115 subjects (44.3%) (Kaplan–Meier estimates of 5-year survival were not explicitly provided). Following multivariate analysis, the independent risk factors for death were ABI < 0.5 (HR 2.29, 95% CI 1.29–4.08), age (HR per increase of 1 year was 1.05, 95% CI 1.02–1.08) and female sex (HR 1.96, 95% CI 1.08–3.56).

Twenty-seven (23.5%) patients underwent major amputation and of these, 20 died by the end of the study. The average time free of amputation was 9.3 ± 3.2 months.

Ghanassia et al.

Ghanassia *et al.* prospectively followed up 89 patients admitted to the hospital for foot ulceration from 1998 to 2000 for a mean follow-up period of 79.4 ± 13.3 months (range 66.1–92.6) (25). The average age was 63.8 ± 10.8 years with 69.7% males. Eleven had type I diabetes, 92.1% had neuropathy, 84.3% had ischaemic wounds and 16.9% underwent lower extremity vascular surgery. Forty-six (51.7%) patients died (5-year survival rate was not provided); 23 with a cause of death of cardiovascular origin, wound-related event in 9, malignancy in 7 and other causes in 7. Increased age, renal impairment and history of amputation were found to be significant in the univariate analysis but only renal impairment remained a significant risk factor following multivariate analysis (HR 4.57, 95% CI 1.1–19.4).

Of the 89 patients, 30 underwent minor amputation and 9 underwent major amputation. Following multivariate analysis, only popliteal stenosis was found to an independent predictor of amputation (HR 3.67, 95% CI 1.34–10.07).

Winkley et al.

Winkley *et al.* followed up 253 diabetic patients for 5 years, with their first ulceration being detected during 2001–2003 (33). The goal was to identify the impact of depression on mortality. The mean age was 62 ± 13.9 years, with 63.6% males and 83% patients with type II diabetes. The mean glycosylated haemoglobin was 8.2% ± 1.7%. Of the total 253 patients, 193 (76.3%) had an ABI >0.9 and 60 (23.7%) had an ABI of 0.5–0.9. In total, 36% patients died within 5 years. Of the 82 depressed individuals, 37 (45.1%) died compared with 55 of the 171 (32.2%) patients without depression. Cox regression showed 5-year mortality to be associated with age (HR 1.06, 95% CI 1.04–1.08), mean glycosylated haemoglobin level (HR 0.86, 95% CI 0.74–1.00), minor depression (HR 1.93, 95% CI 1.00–3.74) and major depression (HR 2.18, 95% CI 1.31–3.65).

Pinto et al.

Pinto *et al.* prospectively followed up 102 diabetic patients with ulceration and 123 diabetic patients without ulceration, who presented between 1995 and 2002, until 2006 to identify the 5-year mortality rate secondary to cardiovascular events (31). The mean age of patients with an ulcer was 66.7 ± 9.8 years and the mean age of those without an ulcer was 66.9 ± 13 years. The ulceration and non-ulceration groups had 55.8% and 54.4% males, respectively. All the patients had type II diabetes. ABI was significantly different between the groups with an average of 0.72 ± 0.2 in the ulceration group compared with 0.89 ± 0.41 in the non-ulceration group. Glycosylated haemoglobin level of >7 was also significantly more prevalent in the ulcer group (63.7%) compared with the non-ulceration group (24.4%).

At 5 years, 13.7% of the patients with ulcerations had died compared with 8.1% of those without an ulceration. Following multivariate Cox analysis, age, duration of diabetes, glycosylated haemoglobin and foot ulceration were shown to be significantly associated with cardiovascular morbidity.

van Baal et al.

van Baal *et al.* reviewed 117 patients with acute Charcot foot and 109 patients with neuropathic ulceration from 1980 to 2007 (32). The mean age in the Charcot group was 58.1 ± 12.5 years, with 63.2% male and 66.7% with type II diabetes. The mean age

in the ulceration group was 58.6 ± 12.5 years, with 67% male and 70.6% with type II diabetes. Renal dysfunction was found in 49/117 Charcot patients and 43/109 ulceration patients. In the Charcot group, the mortality rate was found to be 11% at 1 year, 24% at 3 years and 41% at 5 years. They died at a mean age of 66.4 ± 11.6 years. In the neuropathic ulcer group, the mortality rate was found to be 19% at 1 year, 27% at 3 years and 40% at 5 years. These patients died at a mean age of 66.5 ± 11.2 years. Mortality rate with renal dysfunction was found to be 53.1% in Charcot patients and 62.8% in ulceration patients. This compares with the mortality for Charcot and ulceration patients rates without renal dysfunction, of 26.6% and 27.6%, respectively. Following logistic regression analysis, age and renal dysfunction were shown to be independent predictors of mortality, but Charcot and sex were not. Kaplan–Meier survival analysis showed significantly greater mortality in both Charcot and ulceration groups compared with the general population.

Gazis et al.

Gazis *et al.* retrospectively reviewed new cases of Charcot foot at a specialist diabetic foot clinic in Nottingham, starting in 1982 (30). They had 47 cases of Charcot, which were matched to 47 new-onset neuropathic ulceration cases, based on gender, age, diabetes type, disease duration and year of referral. The mean ages of the Charcot and ulceration groups were 59.2 ± 13.4 and 59.7 ± 12.6 years, respectively. In both groups there were 18 (38.3%) patients with type I diabetes, 26 being males. Diabetes duration was 16.2 ± 11.2 years in the Charcot group and 16.6 ± 11.2 years in the ulcer group. Although PVD was not disclosed, all patients in the ulcer group had at least one palpable pulse. Regarding smoking habit, 7 Charcot and 13 ulcer patients were current or previous smokers. Nephropathy was found in at least 20/45 and 9/32 in the Charcot and ulcer groups, respectively, following removal of missing data. About 44.7% of Charcot patients died at an average time of 3.7 ± 2.8 years compared with 34% who died at an average time of 3.1 ± 2.7 years in the ulceration group. Of the survivors, the average follow-up period was 4.7 ± 4.9 years in the Charcot group and 5.3 ± 3.9 years in the ulcer group. No significant difference was found in mortality. Cause of death in the ulceration group was vascular disease ($n = 5$), pneumonia ($n = 2$), pulmonary embolism ($n = 1$), diabetic ketoacidosis ($n = 1$), liver abscess ($n = 1$) and urinary sepsis ($n = 1$). Four deaths had unknown cause.

Discussion

Making the interpretation of the above collection of studies difficult is their methodological heterogeneity. The assessment of the primary outcome, 5-year mortality, was performed in a variety of ways. Some authors used Kaplan–Meier estimates and Cox regression including other covariates. For those for whom complete follow-up data were available, exact 5-year mortalities were computed. Other authors simply computed a ratio of those whom they knew to have died within 5 years to those enrolled in the study, ignoring censorship. On account of this heterogeneity in reporting, and for the lack of a comparator group, we chose not to more formally estimate the impact of ulceration via meta-analytic techniques.

Further, the sources of data were varied, from retrospective studies to prospective studies and reviews of administrative databases. Each design comes with its own drawbacks and strengths, but they may not be directly comparable. Patients were enrolled or included in studies for a variety of reasons: new-onset ulcers, current ulcers, hospitalisation for ulceration, and so forth, and in different settings including both inpatient and outpatient clinics.

Other covariates that may be of central importance, specifically PVD, were not consistently recorded and were defined in varied ways, from study to study.

With the exception of Faglia *et al.*, most studies had patients whose age ranged between mid-60s and mid-70s (24). All the studies had relatively large samples of patients with ulceration, ranging from 30 or so to ∼2000. In all the studies, males accounted for 50% to about 70% of the study population, except for the case of Sohn *et al.*, where 90% of the patients were males (28). Proportions of type I diabetes were not always recorded, but were relatively low, with a maximum of about 45%.

Collectively, 5-year mortality for diabetic patients with foot ulcers tended to be in the 40% range, but also rose to 63% in those with an ulcer of a limb that was subsequently amputated (34). Promisingly, however, Young *et al.* noted that an aggressive programme of cardiovascular risk management could help reduce mortality rates to as low as 26% (29). This study addresses the education of clinicians, and the importance of a team approach to health care: primary care, podiatry, cardiology and vascular surgery. Further, at least part of the underlying aetiology of the disease, not the symptoms such as ulceration, is being directly addressed using this approach. An even more inclusive approach that includes patient education and the use of appropriate foot wear is suggested by Lavery *et al.* (37). It is worth considering whether a team-based approach, including patients, would help resolve many of the issues related to ulceration and amputation in diabetic patients.

One notable exception to the above is the study of Pinto *et al.*, whose mortality rate was a surprisingly low 13.7%. The mortality rate among their patients with only diabetes was also low, at 8.1%. It is not entirely clear why their rates were so low.

Among the studies identifying risk factors for death, many found increased age, male sex, renal disease, presence or history of ulceration, presence or history of amputation, PVD, longer diabetes duration and poor glycaemic control to be associated with death. However, not all studies identified these factors to be significant. Furthermore, one study (Faglia *et al.*, 2001) found female sex to be associated with death (24). Once again heterogeneity of methodology and definitions may be partially responsible for the variability of findings.

Conclusion

Diabetes and its associated morbidities are a growing concern worldwide, in particular in the USA. Our interest is on the outcomes after lower extremity ulceration in diabetic patients. A great deal of emphasis is placed on limb salvage in diabetic patients suffering from lower extremity ulceration. This recognises the life-changing impact of amputation on these patients.

These efforts are also in part spurred by the impression that amputation in such patients may be a proximal cause of death.

Our goal is to attempt to understand the interrelationships between ulceration, subsequent amputation and eventual death. Does amputation actually shorten lifespan after ulceration, or is this impression simply because of amputation being a proxy for more severe underlying disease, thus presenting researchers with a lead time or length time bias? In this article, we looked to assess the timing of death in diabetic patients presenting with ulceration, preferably with an initial ulcer, and preferably within a short time after the onset of the ulcer.

While our patient populations did have widely varying demographics, they were consistently in their mid-60s and were predominantly suffering from type II diabetes. Males were the majority of patients. The 5-year mortality rates after ulceration were around 40%. Risk factors commonly identified as being associated with death included increased age, male gender, PVD and renal disease.

While not resolving the causal tangle between diabetes, PVD, amputation, ulceration, and death, we can at least begin to understand the association between ulceration and death. Further reviews will dig deeper, looking at the association between amputation and death, and between ulceration and amputation.

Perhaps most encouraging of what we have seen in our review, the article of Young *et al.* gives hope that an aggressive approach to the underlying disease may save lives. If we follow their lead, we may obviate the need to understand whether it is diabetes, ulceration or amputation that cause or are most closely associated with mortality.

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