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DIABETIC Medicine

RESEARCH: COMPLICATIONS

Mortality in 98 type 1 diabetes mellitus and type 2 diabetes mellitus: Foot ulcer location is an independent risk determinant

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Abstract

Introduction: We previously demonstrated in both a longitudinal study and in meta-analysis (pooled relative-risk RR, 2.45) that all-cause mortality is significantly higher in people with diabetes foot ulceration (DFU) than with those without a foot ulcer. In this prospective study, we looked at the factors linked to mortality after presentation to podiatry with DFU.

Methods: Ninety-eight individuals recruited consecutively from the Salford Royal Hospital Multidisciplinary Foot Clinic in Spring 2016 were followed up for up to 48 months. Data concerning health outcomes were extracted from the electronic patient record (EPR).

Results: Seventeen people (17) had type 1 diabetes mellitus, and 81 had type 2 diabetes mellitus. Thirty-one were women. The mean age (range) was 63.6 (28–90) years with maximum diabetes duration 45 years. Mean HbA1c was 72 (95% CI: 67–77) mmol/mol; 97% had neuropathy (International Working Group on the Diabetic Foot (IWGDF) monofilament); 62% had vascular insufficiency (Doppler studies); 69% of ulcers were forefoot, and 23% of ulcers were hind foot in location.

Forty of 98 (40%) patients died in follow-up with 27% of death certificates including sepsis (not foot-related) and 35% renal failure as cause of death. Multivariate regression analysis indicated a 6.3 (95% CI: 3.9–8.1) fold increased risk of death with hind foot ulcer, independent of age/BMI/gender/HbA1c/eGFR/total cholesterol level.

Conclusion: This prospective study has indicated a very high long-term mortality rate in individuals with DFU, greater for those with a hind foot ulcer and shown a close relation between risk of sepsis/renal failure and DFU mortality, highlighting again the importance of addressing all risk factors as soon as people present with a foot ulcer.

KEYWORDS

diabetes, foot ulcer, location, mortality, prospective

1 | INTRODUCTION

Foot ulceration is a major complication of both type 1 diabetes and type 2 diabetes. We and others have presented evidence that people with diabetes foot ulceration (DFU) have a higher mortality rate than diabetes alone.[1-4] This excess mortality remained even after adjusting for other co-morbidities.[5]

A recent meta-analysis by Suluja et al. reported a 2.45 times higher pooled relative risk of all-cause mortality in those with DFU compared with individuals without.[6] The excess mortality was likely attributable to greater event rates of fatal cerebrovascular and cardiovascular disease in those with diabetic foot ulcers. There is a strong association between increased mortality with increasing socio-economic disadvantage in people with diabetes.[7-10] Wound healing however was largely dependent on vascular status and the characteristics of the foot ulcer.[11]

In this study, we looked at the factors linked to mortality after individuals with diabetes presented to a specialist Multidisciplinary Foot Clinic.

Novelty statement

- We previously demonstrated in both a longitudinal study and in meta-analysis (pooled relative-risk RR, 2.45) that all-cause mortality is significantly higher in people with diabetes foot ulceration (FU) than with those without FU. In this prospective study, we looked at the factors linked to mortality after presentation to podiatry with diabetes FU.
- We found a very high long-term mortality rate in individuals with DFU, greater for those with a hind foot ulcer and shown a close relation between risk of sepsis/renal failure and DFU mortality.

2 | METHODS

Salford Royal NHS Foundation Trust Hospital is a large teaching hospital in North-West England. It is a tertiary referral centre. The hospital provides preventative foot care and multidisciplinary management of diabetic foot disease. Within Salford, the whole podiatry team is part of the multidisciplinary Foot Care Team (MDFC). This is an integrated team across primary and secondary care. Furthermore, a foot protection service (FPS) is provided in the community care setting.

Individuals with diabetes are screened for complications within General Practice as per NICE guidelines then risk stratified. Individuals classified as being at risk of foot complications are referred to Salford's Foot Protection Service. This is a life-long service, and all patients with diabetes have open access to this, irrespective of their risk classification. We also provide a daily walk-in emergency service that patients who live in Salford or have registered with a Salford GP can access. Inpatients are also included in the access to our MDFC, in line with Putting Feet First (2016).[12]

People with diabetes foot problems are managed within the foot protection team and escalated into the MDFC clinic if there is an acute episode of active foot disease, such as 'unexplained hot red swollen foot with or without pain', acute Charcot, infection not responding to treatment, osteomyelitis, unexplained pain or limb ischaemia. We then offer a step up, step down service dependent upon foot disease status at any one time.

All patients presenting to the Multidisciplinary Foot Clinic (MDFC) will have had a full holistic, neurological and vascular assessment, assess cardiovascular risk factors and offloading. We use the SINBAD ulcer classification system.[13]

Arterial Doppler studies (Huntley Digital Doppler [Huntleigh Healthcare Ltd, Cardiff, Wales]) and 10 g monofilament examination were carried out. Twenty-eight of 98 individuals had evidence of arterial calcification. Arterial Brachial Index (ABI) was calculated in all patients included in this study.

Our MDFC consists of a Senior Diabetologist, Vascular Surgeon, Consultant Podiatrist, Principal Podiatrist, Consultant Microbiologist and Radiology consultant, supported by a diabetes specialist nurse (DSN) team who arrange follow-up diabetes care within the community setting.

We looked at mortality outcome for 98 individuals presenting consecutively to the Salford Royal Hospital Multidisciplinary Foot Clinic between 6 April 2016 and 26 June 2016. Those people presenting with Charcot arthropathy were excluded. Individuals were followed up for up to 48 months. Data concerning health outcomes were extracted from the Salford Digital Patient (Electronic Patient) record (EPR). Metabolic data and BMI/blood pressure were also extracted from the Salford EPR. As many of the blood samples were non-fasting, we took total cholesterol as a measure of lipid control as this is less influenced by fasting versus non fasting status.

2.1 | Statistics

Data were analysed using the statistical package Intercooled Stata version 14.0 (StataCorp). Data are expressed as mean (95% CI), mean (range), or number (percentage) where relevant. A multiple logistic regression analysis was used to determine the association between measured risk factors and death. The variables included are described in the results

section. Kaplan Meier curves were used to compare survival probabilities for men and women with hind foot versus forefoot ulceration. Chi-squared testing was undertaken to compare categorical variables versus outcome (death). SINBAD score was compared by ANOVA.

There was no loss of individuals to follow-up.

3 | RESULTS

3.1 | Description

Of the 98 individuals, 17 had type 1 diabetes mellitus, and 81 had type 2 diabetes mellitus. Thirty-one were women. The mean age (range) was 63.6 (28–90) years with range of diabetes duration 1–45 years.

Mean duration of diabetes at presentation was 14 (95% confidence interval [CI] 12–16) years. Mean HbA1c was 72 (95% CI: 67–77) mmol/mol. Seventy-nine individuals had an eGFR of <90 ml/min/1.73 m^2; 48% of the people with type 2 diabetes mellitus were treated with insulin.

Out of the group, 17 were current smokers, and 37 were ex-smokers; 14/98 had previously undergone an amputation. Fourteen patients had critical limb ischaemia at presentation, including one with type 1 diabetes and 13 with type 2 diabetes mellitus. Not all 98 people had a foot ulcer location that could be classified as rear foot or hind foot. Therefore, these individuals were excluded from the final analysis.

The forefoot ulcer patients were slightly older and had a higher body mass index (BMI) and higher eGFR with lower HbA1c, than the hind foot ulcer patients (Table 1). There was no significant difference in total cholesterol or HDL-cholesterol between the forefoot and hind foot groups nor in the % with albuminuria or in systolic/diastolic blood pressure; 81% of forefoot ulcer patients were taking statins and 83% of hind foot ulcer patients were on a statin. Anti-platelet agents were taken by 32% of forefoot ulcer patients and 31% of hind foot ulcer patients.

The characteristics of the type 1 diabetes mellitus and type 2 diabetes mellitus patients are shown in Table 2. The type 1 diabetes mellitus patients were younger but had a longer duration of diabetes than those with type 2 diabetes mellitus. The type 1 diabetes patients had on average a higher HbA1C, lower HDL cholesterol and significantly lower BMI.

3.2 | Infection rates at presentation

We used the Infectious Diseases Society of America (IDSA) 2012 classification[14] for classification of ulcer infection. In relation to the IDSA classification, of the 98 ulcers, 32 were not infected, 28 were mildly infected, 24 were moderately infected and 14 were severely infected at the time of presentation.

Osteomyelitis was present in 18/98 cases at baseline.

3.3 | Peripheral neuropathy and vascular insufficiency

Ninety-seven per cent of the individuals followed up had evidence of peripheral neuropathy on the basis of the International Working Group on the Diabetic Foot (IWGDF) monofilament guidance[15] at the time of presentation; 62% of these studies had evidence of vascular insufficiency (Arterial Doppler studies) at the time of presentation; 69% of ulcers were forefoot in location (including toe ulcers), and 24% were hind foot in location (including heel ulcers). Eight per cent of ulcers were located above the foot; 17% of people had a history of previous foot ulceration.

Four of the hind foot ulcer patients and seven of the forefoot ulcer patients were taking an SGLT2-inhibitor, whereas three of each group were taking a GLP-1 agonist (daily at the time of initial presentation).

3.4 | Treatment

Duration of antibiotic treatment was 12 weeks (minimum) for hind foot ulcers versus 6 weeks (minimum) for forefoot ulcers. Surgical intervention in the form of debridement at initial presentation was undertaken in 6% of cases of forefoot ulcer at presentation and in 8% of hind foot ulcers. Offloading measures employed included Derby sandal, total contact inlay, rear foot off loader, forefoot off loader and Tener boot. Patient concordance with offloading devices was good.

In relation to complete wound healing, 76% of patients achieved this over a period of up to 9 months.

There were there no differences in time to heal of osteomyelitis based on the location of the ulcer. Sixteen per cent had recurrent ulceration over the period of follow-up.

TABLE 1 Comparison of anthropometric and metabolic variables by foot ulcer location (Mean +/- 95% Confidence Interval) (CI))

Location	Results (n)	Age (years)	Total Cholesterol (mmol/L)	HDL (mmol/L)	EGFR (ml/min/1.73 m^2)	BMI (kg/m^2)	HBA1c (mmol/mol)
Forefoot	64	64.6 (61.2–68.0)	4.12 (3.87–4.36)	1.17 (1.07–1.26)	61.8 (56.1–67.4)	30.9 (29.1–32.7)	71.5 (64.9–78.0)
Hind foot	25	60.9 (55.0–66.8)	3.99 (3.55–4.42)	1.25 (1.10–1.40)	53.8 (42.9–64.7)	28.9 (25.6–32.1)	74.9 (65.1–84.8)

TABLE 2 Characteristics of the Type 1 diabetes and Type 2 diabetes patients

	Type 1 Diabetes	Type 2 Diabetes
Proportion of women (%)	29.4%	32.5%
Age of diagnosis of diabetes (years)	27.8 ± 16.5	54.6 ± 15.2
Duration of diabetes (years)	23.2 ± 14.2	12.0 ± 7.7
Age in 2016 (years)	37.8 ± 16.5	54.6 ± 15.2
BMI (kg/m^2)	23.8 ± 2.7	31.5 ± 7.4
HbA1c (mmol/mol)	81.2 ± 21.1	69.2 ± 25.6
eGFR (ml/min/1.73 m^2)	53.1 ± 28.2	60.4 ± 22.6
Cholesterol (mmol/L)	4.1 ± 1.2	4.1 ± 0.9
HDL cholesterol (mmol/L)	1.4 ± 0.3	2.6 ± 11.7
Smoker %	23.5	16.3
Treated with insulin (%)	93.8	48.1
Mortality (%)	35.3	42.5

All data are presented as mean ± SD or percent unless otherwise stated.

TABLE 3 Multivariate logistic regression analysis: independent factors included

Variable	Odds ratio	*p* value	[95% Conf. Interval]
Foot ulcer location	6.34	0.041	3.92–8.31
Age (years)	1.06	0.061	0.99–1.12
Gender	1.17	0.824	0.28–4.84
Hba1c (mmol/mol)	0.99	0.488	0.95–1.02
eGFR (ml/min/1.73 m^2)	0.97	0.041	0.94–0.99
Osteomyelitis	0.78	0.735	0.18–3.39
Cellulitis	0.20	0.406	0.01–8.94
BMI (kg/m^2)	0.95	0.242	0.86–1.04
Vascular	0.46	0.354	0.09–2.37
Cholesterol (mmol/L)	1.11	0.091	0.95–1.25
Smoking (1 = smoking)	1.22	0.082	0.92–1.35
Neuropathy	1.05	0.103	0.92–1.20

Nine of 98 patients required revascularization (over the follow-up period).

3.5 | Cause of death

Mortality rate over 4 years of follow-up was 35% for the type 1 diabetes mellitus patients with a foot ulcer and 43% for the type 2 diabetes patients.

In relation to cause of death (sometimes more than one cause of death was listed), over the follow-up period, 40 (40%) people died with 27% of death certificates including sepsis (not foot-related) as a cause—sepsis specifically included urosepsis in 5% of the deaths. Renal failure was listed as cause of death in 35% of cases. Myocardial infarction/ischaemic heart disease was listed in 25% of cases and cancer in 5% of cases. Pneumonia was recorded as a cause of death in 30% of cases.

Logistic regression (stepwise backwards) analysis was carried out. In the regression model, we included the variables shown in Table 3. This indicated a 6.34 (95% CI: 3.92–8.31) fold increased risk of death with a hind foot ulcer, independent of eGFR (odds ratio 0.97 [0.94–0.99]) (lower eGFR was associated with greater risk of death), age, BMI, gender, HbA1c, presence of cellulitis, presence of osteomyelitis, total cholesterol level, vascular insufficiency, documented neuropathy and smoking (Table 3). Smoking status refers to current smokers only.

The relative rate of death for hind foot versus forefoot ulcers is shown in Figure 1. The mortality rate was higher for hind foot ulcers from 6 months after initial presentation. We found no significant relation between the ulcer type (neuropathic, ischaemic or neuroischaemic) and mortality ($\chi^2 = 0.12$, $p = 0.733$). There was no difference between the hind foot and forefoot ulcers in SINBAD score. A higher SINBAD score was associated with higher mortality rate ($F = 3.4$, $p = 0.01$). Osteomyelitis was not specifically linked to mortality ($\chi^2 = 0.35$, $p = 0.552$).

4 | DISCUSSION

This prospective study has indicated a very high long-term mortality rate in individuals with presenting to a specialist podiatry clinic, greater for those with a hind foot ulcer and shown a close relation between risk of sepsis/renal failure and diabetes FU mortality. This level of mortality was seen, even

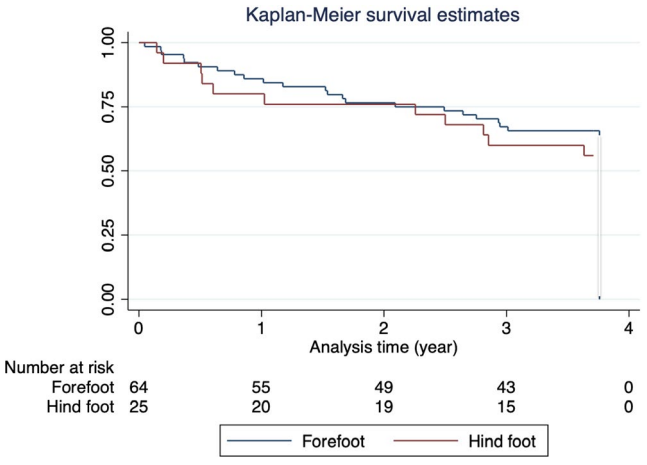

FIGURE 1 Kaplan Meier survival curve for death as outcome for hind foot versus forefoot location of the ulcer

though patients were attending a specialist Multidisciplinary Foot Clinic where a Consultant Diabetologist and Consultant Vascular Surgeon, Consultant Podiatrist and Consultant Microbiologist are in attendance. This again highlights the importance of addressing all risk factors as soon as people present with a foot ulcer. Furthermore, risk of death was 6.3 times higher in people with a hind foot ulcer.

The presence of urosepsis as a contributory cause of death in many cases may relate to the fact that foot ulceration often occurs in people with suboptimal glycaemic control which itself can lead to impaired neutrophil function[16] and consequently to a greater likelihood of a urinary tract infection progressing to full blown urosepsis. This also relates to pneumonia being recorded as a cause of death in 30% of cases.

The increased mortality rate associated with hind foot versus forefoot ulcers highlights the more serious nature of ulcers at that location likely associated with poorer tissue perfusion in patients with such an ulcer location. Also, hind foot ulcer is a marker of poorer overall health with reduced mobility being a consequence of that poorer overall health. This accords with the findings of the National Diabetes Foot Care Audit[17] which indicated more adverse outcomes in term of amputation and death when a hind foot ulcer is present. The association of a higher SINBAD score with increased mortality accords with the findings of the National Diabetes Food Audit.[17]

It has been demonstrated that 5-year mortality for diabetes with foot ulceration is around 40%.[18,19] The results of our study (just under 4 years follow-up) are of a similar order of magnitude to this. It is likely that higher mortality rates observed occur as a result of cardiovascular and non-cardiovascular complications of diabetes such as sepsis[20] as we have found here. A study by Young et al. showed that an aggressive program of cardiovascular risk management can reduce mortality rates to as low as 26% in individuals with diabetic foot ulceration.[21]

Previous studies have shown increased mortality associated with heel ulcers. In the European Study Group on Diabetes and the Lower Extremity (EURODIALE) study, ulcer location had a significant effect on the outcome. Both time to healing and mortality was highest in individuals with heel ulcers. Compared with those with mid-foot and forefoot ulcers.[22] Also, significantly more people with heel ulcers are unable to stand or walk without help compared with those with forefoot and mid foot ulcers. Such immobility, as well as being associated with the ulcer itself, is probably related to co-morbidities including renal failure, of which there was a trend in the heel ulcer group. Location of foot ulcer is known to contribute to poor physical functioning.[22,23]

In relation to infrapopliteal arterial disease, in a further study, those people with an ischaemic heel ulcer were at increased risk of mortality compared with those with a forefoot ulcer. One-year and 3-year amputation free survival was 66% and 44% for forefoot wounds and respectively 48% and 21% for heel wounds.[24,25]

Our results accord with the findings of the National Diabetes Foot Care Audit and the prospective study of Jeyaraman et al[5,14] both of which indicated more adverse outcomes in terms of amputation and death when a hind foot ulcer is present. Overall, patients with hind foot ulcers suffer from diminished general health and prolonged immobility and die from their co-morbidities, including renal failure and cardiovascular disease. A summary of recent studies describing mortality rates in people with diabetes foot ulceration is given in a recently published meta-analysis.[6]

The occurrence of a diabetes foot ulcer has a marked impact on the person's activity level, and when combined with slow resolution, the condition is understandably linked with a reduction in quality of life.[26] With regard to the incidence of depression, reports are mixed. One group reported that incident first ulcers are associated with depression and that this is independently associated with mortality at 5 years.[27] However, other investigators have reported that both quality of life and depressive symptoms are reversed by healing—either with or without amputation.[28,29]

The findings of our study suggest that in people with diabetes, hind foot ulcers must be seen as a harbinger of more adverse outcomes than foot ulcers at other sites, with tight control of glycaemia and focused management of cardiovascular and renal parameters being a priority, in addition to regular specialist podiatry input. We believe that the findings here can be generalised to other parts of the United Kingdom and beyond, because of the broad demographic range of our patient group, coming as they do from all over the Greater Manchester conurbation.

4.1 | Limitations/Strengths of our study

Our dataset is limited by the number of patients who presented in the recruitment time frame at a single centre. Another limitation of the study is the relatively small numbers compared with previously done prospective studies in this regard, though the relatively robust and long duration of follow-up somewhat offsets this limitation. Screening for signs of autonomic neuropathy (given its association with increased mortality rate)[30] would have provided an additional relevant variable for the multiple regression analysis. We accept that this is the limitation of the study, and further work in this area will include tests for autonomic neuropathy.

A further limitation is the lack of a control population of diabetes without foot ulcers. Nevertheless, this is a prospective evaluation of outcome using data available from the Salford EPR, and follow-up was for a period of up to 4 years.

5 | CONCLUSION

This prospective study has indicated a very high long-term mortality rate in individuals with DFU, greater for those with a hind foot ulcer and shown a close relation between risk of sepsis/renal failure and DFU mortality.

This again highlights the importance of addressing all risk factors as soon as people present with DFU to their family doctor or specialist service. All measures must be taken to achieve and sustain good glycaemic control following presentation with a diabetes foot ulcer.

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CONFLICT OF INTEREST

All authors have no competing interest to declare.

AUTHOR CONTRIBUTIONS

Heather Schofield collected all the data for the project and designed the follow-up protocol. Adrian Heald and Simon Anderson co-wrote the paper and performed the data analysis with contributions from Heather Schofield and Samantha Haycock. Adam Robinson provided editorial input and context overview.

DATA AVAILABILITY STATEMENT

Any requests for data extracts will be considered by Dr. Heald as the corresponding author.

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