Influence of foot ulceration on cause-specific mortality in patients with diabetes mellitus

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Objective: **The purpose of this study was to assess the odds of all-cause mortality in individuals with diabetic foot ulceration (DFU) compared with those with diabetes and no history of DFU. In addition, we sought to determine the strength of association of DFU with cardiovascular and nonvascular mortality.**

Methods: **We obtained data for a cohort of patients who attended a secondary care diabetic foot clinic or a general diabetes clinic between 2009 and 2010. A clinic cohort of patients with diabetes and no history of DFU provided a control group. Cause-specific mortality was recorded during a median follow-up duration of 3.6 years (interquartile range, 3.3-4.2 years). The association between DFU and all-cause mortality was evaluated by Cox regression. The association between DFU and cardiovascular mortality was determined by competing risk modeling.**

Results: **We recorded 145 events of all-cause mortality and 27 events of cardiovascular mortality among 869 patients with diabetes. After adjustment for potential confounders, DFU was associated with both cardiovascular disease (hazard ratio, 2.53; 95% confidence interval, 0.98-6.49; $P = .05$) and all-cause mortality (hazard ratio, 3.98; 95% confidence interval, 2.55-6.21; $P < .001$). The proportion of deaths attributable to cardiovascular disease was similar between the groups (18% with diabetes only and 19% with DFU; $P = .91$).**

Conclusions: **DFU is associated with premature death from vascular and nonvascular causes. (J Vasc Surg 2014;60:982-6.)**

Diabetes mellitus (DM) is an established risk factor for several causes of death, including ischemic heart disease, stroke, renal disease, infectious diseases, and several cancers.[1,2] Estimates based on analysis of 123,205 deaths among 820,000 people suggest an adjusted hazard ratio (HR) of 1.80 (95% confidence interval [CI], 1.71-1.90) for death from any cause compared with persons without diabetes.[1] Evidence is also emerging that diabetic foot ulceration (DFU) carries an even greater risk of premature death. A meta-analysis of 3619 deaths among individuals with DM and those with a history of DFU reported a higher risk of all-cause mortality in patients with DFU (relative risk, 1.89; 95% CI, 1.60-2.23).[3] This excess risk was attributable, in part, to a greater burden of cardiovascular disease (CVD), with greater event rates for both fatal cerebrovascular accident (five vs four per 1000 person-years) and fatal myocardial infarction (17 vs 12 per 1000 person-years) in the DFU group compared with the DM group. Importantly, this meta-analysis was limited by a lack of individual patient data to establish the impact of CVD risk factors on cause-specific mortality.

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Author conflict of interest: none.

Additional material for this article may be found online at www.jvascsurg.org.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214/$36.00

http://dx.doi.org/10.1016/j.jvs.2014.04.052

Some uncertainty therefore exists about the relationship between DFU and cause-specific mortality, including the strength of association between DFU and nonvascular causes of death. We hypothesized that DFU might signal an increased risk of cardiovascular mortality among patients with diabetes, accounting in part for an excess risk of death from all causes. The purpose of this study was to evaluate differences in overall mortality and mode of death among adults with diabetes, with and without a history of foot ulceration. Specifically, we sought to assess the following: (1) the odds of all-cause mortality in individuals with DFU compared with those with diabetes and no history of DFU; and (2) the relative contribution of CVD and nonvascular deaths to any excess odds in overall mortality.

METHODS

Patients. A single-center cohort of all patients attending a diabetic foot clinic between January 2009 and December 2010 was studied retrospectively. In the United Kingdom, patients with DFU are referred from the community into secondary care foot clinics and managed according to current guidelines provided by the National Institute for Health and Care Excellence,[4] as part of an established care pathway. In the present study, patients were managed by a multidisciplinary team involving specialist diabetes physicians, microbiologists, vascular surgeons, and podiatrists. Patients are typically reviewed in the foot clinic weekly until complete healing is achieved. Our control group consisted of patients with DM attending a general diabetes clinic during the same period. Data were extracted for consecutive patients attending the general diabetes clinic until the number of patients in the control group matched those in the DFU group. Patients

attending the general diabetes clinic are typically reviewed biannually to optimize blood glucose control, to evaluate and manage the development of complications of diabetes, and to institute appropriate CVD risk management. Cardiovascular risk in patients from both clinic populations was managed according to current guidelines at the time of the clinic visit.[5,6] Demographic data, cardiovascular risk factors, and prescribing information were recorded from clinic letters, case notes, and electronic hospital records.

Inclusion criteria specified patients ≥18 years of age with a confirmed diagnosis of diabetes, verified by diagnostic tests, hypoglycemic therapy, or medical records review. Diagnostic criteria for DM were consistent with the American Diabetes Association definition: fasting plasma glucose concentration ≥126 mg/dL or use of hypoglycemic therapy.[7] Patients included in the foot ulcer group had active ulceration at baseline; however, this did not necessarily represent the first diagnosis of DFU. Patients in the DM group with a documented history of foot ulceration were excluded from all analyses. A foot ulcer was defined as a full-thickness skin defect that was observed during three consecutive visits to the multidisciplinary foot clinic. Ischemic heart disease was defined by previous myocardial infarction or unstable angina and coronary revascularization by a previous coronary angioplasty or coronary artery bypass grafting procedure. Stroke was defined by a documented history of ischemic stroke (not including transient ischemic attack). Peripheral arterial disease (PAD) was defined by a history of intermittent claudication or rest pain, the absence of two foot pulses, or an abnormal ankle-brachial pressure index ($<$ or $>$ 0.9 to 1.1) or confirmed by duplex ultrasound, computed tomography angiography, or angiography. Congestive cardiac failure was defined by left ventricular systolic dysfunction on echocardiography or documented history of heart failure.

Cause of death. Cause of death was ascertained by review of death certificates and verified against case notes and electronic hospital records. Primary care physicians were contacted by phone if there was doubt about the cause of death when deaths occurred in the community. DFU-related deaths were defined as those directly related to the foot ulcer (eg, sepsis secondary to DFU) and deaths resulting from complications after admission to the hospital or within 30 days of admission to the hospital for DFU (eg, organ failure resulting from sepsis, complications of procedures to treat DFU). The causes of death were classified into CVD-specific mortality and non-CVD mortality according to the International Classification of Diseases, Ninth Edition. The direct cause of death or underlying disease was considered only; diseases in the pathway to death (secondary causes) were ignored in ascertaining cause of death for analysis. Causes of death were determined by J.B. and M.G., and any disputes were resolved by the senior author (R.H.).

Statistical analysis. Continuous variables are expressed as mean ± standard deviation; categorical variables are presented as percentages. Differences between groups were assessed by a combination of χ^2 test and unpaired *t*-tests, for categorical and continuous data, respectively. To test the association between DFU and all-cause mortality, Kaplan-Meier curves were developed with 95% CIs and standard errors. Patients lost to follow-up were censored on the date of last known follow-up. Survivors were censored at the end of follow-up when individual mortality data were ascertained. Cox proportional hazards regression was used to obtain the HRs and 95% CIs for all-cause mortality. Potential confounding variables were selected on the basis of established evidence demonstrating their association with all-cause mortality. In the adjusted model for all-cause mortality, we considered the following potential confounders: demographics (age, gender), cardiovascular factors (hypertension, dyslipidemia, smoking history, antihypertensive medication use, and history of CVD), comorbidities (chronic kidney disease stage 3-5, chronic obstructive pulmonary disease, history of neoplasm), diabetes-specific variables (duration of diabetes, hemoglobin A_{1c}, insulin use, and use of oral antihyperglycemic medication), and incident revascularization or major amputation procedure. Cardiovascular and nonvascular mortality estimates were calculated from the cumulative incidence of competing risks from baseline by the Fine and Gray method.[8] The Cox regression analysis, modified for competing risks for cardiovascular and nonvascular mortality, identified univariable and multivariable associations with outcome for each group. Variables considered in univariable analysis for cardiovascular mortality included demographics (age, gender), history of myocardial infarction, coronary revascularization, stroke, PAD, congestive cardiac failure, smoking, hypertension, hypercholesterolemia, chronic kidney disease (stage, 3-5), or antihypertensive use. Variables selected for multivariable analysis were those demonstrating a significant association with each outcome measure at a $P < .5$ level in univariable analysis. To avoid collinearity among variables with strong associations (eg, hypertension, antihypertensive therapy, use of renin-angiotensin blockade), we entered into the multivariable models the variable that had the strongest association with all-cause or CVD mortality. We calculated that a sample size of 800 patients would be more than sufficient to detect increased relative risks between 1.41 and 2.22 for CVD mortality with 80% power,[3] assuming a two-sided test and a significance level of .05. Furthermore, the authors were satisfied that such differences would be clinically meaningful. Statistical analyses were performed with SPSS version 22.0 (SPSS Inc, Chicago, Ill) and R (cmprsk package; r-project.org).

RESULTS

A total of 869 patients were included in the study (436 in the DM group and 433 in the DFU group). Median follow-up duration in the DFU group was 3.7 years (interquartile range, 3.3-4.3 years) compared with 3.6 years (interquartile range, 3.3-4.1 years) in the DM-only group. Mean age was similar between the groups (Table I). Compared with patients with DM only, those in the DFU group were more frequently male with a greater prevalence of CVD, including ischemic heart disease, stroke, and PAD ($P < .01$). Accordingly, patients with DFU