Amputation and Mortality in New-Onset Diabetic Foot Ulcers Stratified by Etiology

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OBJECTIVE — Foot ulcers and their complications are an important cause of morbidity and mortality in diabetes. The present study aims to examine the long-term outcome in terms of amputations and mortality in patients with new-onset diabetic foot ulcers in subgroups stratified by etiology.

RESEARCH DESIGN AND METHODS — Patients presenting with new ulcers (duration <1 month) to a dedicated diabetic foot clinic between 1994 and 1998 were studied. Outcomes were determined until March 2000 (or death) from podiatry, hospital, and district registers. Baseline clinical examination was done to classify ulcers as neuropathic, ischemic, or neuroischemic. Five-year amputation and mortality rates were derived from Kaplan-Meier survival analysis curves.

RESULTS — Of the 185 patients studied, 41% had peripheral vascular disease (PVD) and 61% had neuropathy; 45%, 16%, and 24% of patients had neuropathic, ischemic, and neuroischemic ulcers, respectively. The mean follow-up period was 34 months (range 1–65) including survivors and patients who died during the study period. Five-year amputation rates were higher for ischemic (29%) and neuroischemic (25%) than neuropathic (11%) ulcers. Five-year mortality was 45%, 18%, and 55% for neuropathic, neuroischemic, and ischemic ulcers, respectively. Mortality was higher in ischemic ulcers than neuropathic ulcers. On multivariate regression analysis, only increasing age predicted shorter survival time.

CONCLUSIONS — All types of diabetic foot ulcers are associated with high morbidity and mortality. The increased mortality appears to be independent of factors increasing ulcer risk— that is, neuropathy and PVD—in patients with established foot ulcers.

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F oot ulcers and their complications are an important cause of morbidity and mortality in patients with diabetes. Annual incidence of foot ulcers is 1% to 4% and prevalence 5% to 10% in patients with diabetes (1). About 50% of patients undergoing nontraumatic lower-limb amputations have diabetes (2). These patients have a high mortality following amputation, ranging from 39% to 80% at 5 years (1).

There are relatively few studies on survival of patients with diabetic foot ulcers. Furthermore, many of these studies are based on prevalent cases, which overestimate mortality because ulcers are likely to have been present for months to years before the patients are enrolled. Finally, little is known about the survival of patients with different types of foot ulcers, i.e., neuropathic, neuroischemic, or ischemic.

The present study aims to examine outcomes in patients with new-onset diabetic foot ulcers of various etiologies with reference to amputations and mortality.

RESEARCH DESIGN AND METHODS

— Patients were recruited from the Diabetic Foot Clinic at University Hospital Aintree in Liverpool between 1994 and 1998. All patients with newly diagnosed diabetic foot ulcers (duration <1 month) were enrolled. A chiropodist and a consultant diabetologist assessed all the patients.

Diabetes was defined as type 1 if the age of onset was <30 years and insulin treatment was started at diagnosis. Patients with onset of diabetes after age 30 years and initially on diet or oral hypoglycemic therapy were considered to have type 2 diabetes. A foot ulcer was defined as a full-thickness skin defect present for at least 2 weeks. A standard neurological examination tested the sensation to light touch (cotton wool), pain (sterile neurological examination pins [Neurotips]), vibration (128-Hz tuning fork), and tendon reflexes at the ankle (3). Peripheral neuropathy was considered present if three of the four were absent. Peripheral vascular disease (PVD) was considered present when both the dorsalis pedis and posterior tibial pulses were absent in the affected limb (4). Based on this, ulcers were classified as neuropathic, ischemic, or neuroischemic.

Data on outcome were collected from podiatric and hospital records and district registers up to March 2000 (or death, if earlier). Mortality and lower-extremity amputation events were noted on all the patients from the above sources. Amputation included both major and minor procedures including toe amputations. Statistical analysis was performed using SPSS for Windows (SPSS, Chicago, IL). The unpaired *t* test was used for mean values and the χ^2 test for categorical values. Kaplan-Meier survival curves were generated for the cohort, and the log-rank test was used to test equality of survivor
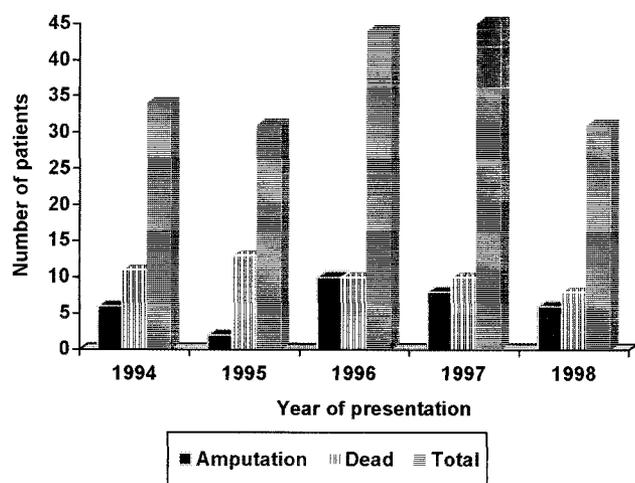
Figure 1—*Number of patients and outcomes (data on outcome until March 2000).*

functions between the various groups. Multinomial and forward stepwise Cox linear regression analysis was used to test for associations between risk factors and outcomes.

RESULTS — Between 1994 and 1998, a total of 185 patients with new ulcers were seen at the Diabetic Foot Clinic (Fig. 1). Of these patients, 118 (64%) were male. The mean age (± SD) at presentation was 65 ± 13 years (range 25–93). The majority of patients had type 2 diabetes (84%), whereas 10% had type 1 diabetes (in the remaining 6%, diabetes type was uncertain from the records). Neuropathy and PVD were present in 113 (61%) and 76 (41%) patients, respectively. Based on this, ulcers were classified as neuropathic, ischemic, and neuroischemic in 83 (45%), 44 (24%), and 30 (16%) subjects, respectively. In 28 patients (15%), there was neither clinical neuropathy nor PVD by the study criteria (Table 1).

The median follow-up period was 28 months (range 1–65), including survivors and patients who died during the study period. A total of 30 patients (17%) had amputations, giving a crude amputation rate of 16%. Mean time free of amputation was 58 months, and the 5-year amputation rate was 19% for the whole group. Patients with PVD had a significantly higher 5-year amputation rate than those without PVD ($P = 0.02$). The 5-year amputation rates were higher for ischemic (29%) and neuroischemic (25%) ulcers than neuropathic ulcers (11%) (Table 2 and Fig. 2).

Mortality trends were also assessed in the same period. Fifty-two patients had died, the mean survival period being 50 months and the 5-year mortality rate 44% for the entire group. Patients who died during subsequent follow-up tended to

be older at presentation (mean age 71 ± 10 years) than those remaining alive (63 ± 13 years; $P < 0.01$). Mortality rates remained similar in both sexes and types of diabetes (Table 1). Again, patients with PVD and ischemic ulcers had a significantly worse outcome, with a mean survival period of 41 months and a 5-year mortality rate of 56%. Five-year mortality was higher in patients who had amputation (47%) than in those without (43%), though this was not statistically significant (Table 3 and Fig. 3)

Cause of death could be ascertained in 26 patients who died in our hospital. Cardiac and cerebrovascular diseases accounted for the majority of deaths (38%), followed by pneumonia (27%), emphysema (8%), malignancy (12%), septicemia (12%), and renal failure (4%).

On multinomial regression analysis, among the variables, only age predicted mortality and none was independently re-

Table 1—*Characteristics at baseline of patients in relation to subsequent mortality*

	Total	Alive (%)	Dead (%)
Patients (*n*)	185	133 (72)	52 (28)
Age (years)	65 ± 13	63 ± 13	71 ± 10*
Sex			
Male	118	83 (70)	53 (30)
Female	67	50 (75)	17 (25)
Diabetes			
Type 1	19	14 (74)	5 (26)
Type 2	155	110 (71)	45 (29)
Unclassified	11	9 (82)	2 (18)
Ulcer type			
Neuropathic	83	62 (75)	21 (25)
Ischemic	44	24 (55)	20 (46)
Neuroischemic	30	24 (80)	6 (20)
Other	28	23 (82)	5 (18)

Data are *n* (%) or means ± SD. *$P < 0.01$.

Table 2—*Five-year amputation rates and time to amputation*

	Cases (*n*)	Amputation (*n*)	Time to amputation (months)	5-year amputation rate (%)
Overall	185	30	58 (55–61)	19
Ulcer type				
Neuropathic (N)	83	8	62 (58–65)*	11†
Neuroischemic (NI)	30	7	54 (44–62)	25
Ischemic (I)	44	11	52 (44–60)‡§	29§
Other	28	4	50 (44–55)	22‖

Data are means (95% CI) unless noted otherwise. *$P = 0.06$ for N vs. NI; †$P = 0.05$ for N vs. NI; ‡$P = 0.06$ for N vs. I; §$P < 0.05$; ‖four-year amputation rate.
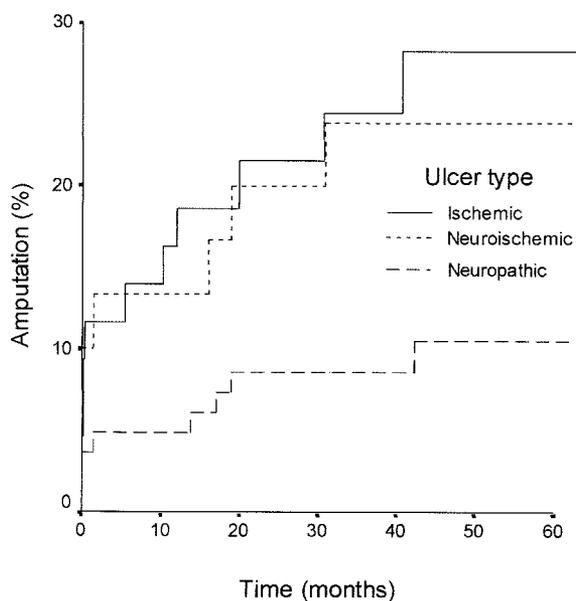
Figure 2—*Cumulative amputation rates in foot ulcers of various etiologies.*

amputation rates of 11.2% in patients with new-onset foot ulcers over a 4-year period. This is in agreement with crude amputation rates (16%), 5-year amputation rates (19%), and mean time to amputation (58 months) in our series. Absence of peripheral pulses has been established to be a risk factor for subsequent amputation (11–16). In our study, 59% of patients who had amputations had PVD. Five-year amputation rates (27%) were higher, and time to amputation (53 months) was less ($P < 0.05$) in these patients. Prevalence of peripheral neuropathy was not significantly more common among amputees. Indeed, time to amputation was greater in those with neuropathy than in those without (Table 2). We believe that those who developed ulcers in the absence of clinical neuropathy were

lated to amputation. Similarly, on multivariate forward stepwise Cox regression analysis to estimate time to outcome, age predicted shorter survival time ($P < 0.01$).

CONCLUSIONS — Foot problems in diabetes continue to challenge the clinicians who care for these patients. Not only are they associated with morbidity and disability, but they also lead to significant impairment of quality of life (5). Although a high mortality is well documented in patients with diabetic foot problems following amputation, few studies have assessed long-term mortality in patients with new-onset diabetic foot ulcers (6).

The study design included only patients with recent-onset foot ulcers, thus avoiding overestimation of disease severity that may occur when prevalent cases are included. We used simple clinical tests to diagnose PVD and neuropathy. These can be easily performed in any hospital or community foot clinic. We regard our results as robust, since a large number of patients with foot ulcers were followed for a substantial period. Mortality rates are likely to be particularly accurate, as we included podiatry records, hospital data, and information from the district mortality register. However, the exact cause of death could be ascertained only if the patient died in our hospital.

Observational studies suggest that 6–43% of patients with diabetes and a foot ulcer eventually progress to amputation (7–9). Ramsey et al. (10) reported

Table 3—*Mean survival period and 5-year mortality*

	Cases (n)	Deaths (n)	Survival (months)	5-year mortality (%)
Overall	185	52	50 (47–54)	44
Ulcer type				
Neuropathic (N)	83	21	52 (48–57)	45
Neuroischemic (NI)	30	6	53 (45–61)*	20
Ischemic (I)	44	20	41 (34–49)†‡	56†‡
Other	28	5	46 (42–51)	23§
Amputation	30	9	50 (42–58)	47
No amputation	153	43	50 (46–54)	43

Data are means (95% CI) unless noted otherwise. *$P = 0.05$ for I vs. NI; †$P < 0.05$ for I vs. N; ‡$P < 0.05$; §three-year mortality.
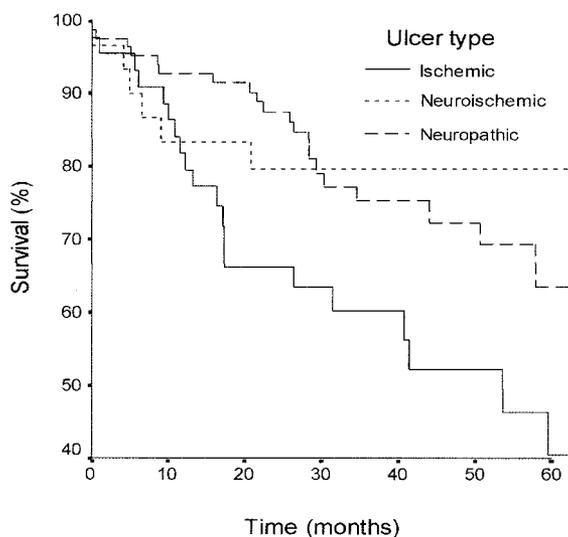

Figure 3— *Cumulative survival rates in foot ulcers of various etiologies.*

more likely to have PVD as a confounding variable.

Patients with foot ulcers were noted to have high mortality rates in our study (mean survival period 50 months and 5-year mortality rate 44%). Boyko et al. (17) reported a relative risk of death of 2.39 among diabetic patients developing new foot ulcers and commented that overall high mortality in all the ulcer subtypes suggests that diabetic foot ulcers may serve as a marker of as-yet-unknown conditions increasing mortality. Most authors have found higher mortality in diabetic patients with previous amputation (8,11,18). In our series, five-year mortality among amputees (47%) was not significantly greater than among those without amputation (43%). Like us, Ramsey et al. (10) did not find higher mortality among 80 patients who had amputations in a group of 514 patients with diabetic foot ulcers.

Few studies have addressed the issue of survival among patients with different types of diabetic foot ulcers. In a cohort of diabetic patients having local foot surgery, only 11% of those with arteriopathy, versus 58% of those without PVD, survived after a median follow-up of 92 months (19). Similar results were noted in a study at King's College, London (20). In our study, patients with ischemic ulcers had a higher 5-year mortality (56%) than those with neuropathy (45%; *P* = 0.01). Indeed, on paired comparisons in our and most other series, presence of PVD is significantly associated with reduced survival in foot ulcer patients (17–20). This is likely to be due to associated atherosclerotic vascular disease in the coronary and cerebral circulations. However, mean age at presentation of ischemic ulcer patients was about 8 years more than that of neuropathy patients, and on the multinomial regression analysis model, only increasing age was found to predict mortality. Thus, the higher age of patients with ischemic ulcers acts as a confounding variable.

Three-year mortality and amputation rates of 23% and 22%, respectively, were noted among patients who did not have neuropathy or PVD. It is likely that these patients had underlying PVD or neuropathy not detected by the clinical criteria. Either way, our results prove that any patient with a diabetic foot ulcer is at high risk of amputation and death irrespective of underlying etiology and deserves aggressive management.

In summary, this study confirms the high mortality of patients with diabetic foot ulcers in addition to the associated substantial morbidity and disability. The mortality appears to be independent of factors increasing ulcer risk, i.e., neuropathy and PVD, in patients with established diabetic foot ulcers. An aggressive multidisciplinary approach is warranted not only to manage foot problems in such patients but also to recognize and reduce risk of death from other comorbid conditions to save both limb and life.

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