Rate of Healing of Neuropathic Ulcers of the Foot in Diabetes and Its Relationship to Ulcer Duration and Ulcer Area

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OBJECTIVE — To examine the outcome of neuropathic foot ulcers and to seek associations between healing and features of the ulcers at baseline.

RESEARCH DESIGN AND METHODS — Data were collected prospectively during the course of routine management. All patients were selected who presented to a single unit between 1 January 2000 and 31 December 2004 with neuropathic foot ulcers and without evidence of either peripheral arterial disease or infection. Associations were sought between ulcer characteristics at baseline and clinical outcome.

RESULTS — A total of 154 patients (66.9% male) presented with 410 ulcers. Age was 57.4 ± 12.0 years (means ± SD). A total of 178 (43.4%) ulcers were on the plantar aspect of the foot; 73.7% of ulcers had a cross-sectional area of <1 cm^2. Median ulcer duration at referral was 15 days (range 1–1,046). Healing without amputation was observed in 91.7%. The percentage of ulcers healed at 12, 20, and 52 weeks were 59.3, 70.5, and 86.6%, respectively. Significant associations were observed between area at referral and outcome type (χ^2 $P < 0.0001$), prior ulcer duration (Kruskal-Wallis $P = 0.006$), and time to healing (Kruskal-Wallis $P = 0.014$), as well as between ulcer duration and time to healing (Spearman ρ, $r = 0.104$, $P = 0.047$). There was no difference between plantar and nonplantar ulcers.

CONCLUSIONS — The rate of healing in this cohort provides a benchmark for comparison with other centers. While further work is needed to determine how outcomes can be improved in unselected series such as these, the confirmation of close relationships between ulcer duration at referral, ulcer area, and outcome emphasizes the importance of early expert assessment of newly occurring neuropathic ulcers.

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While there is evolving consensus on the best management of different types of diabetic foot disease, there remain differences in clinical practice between different expert centers, and it is important to determine whether these differences are associated with better or worse clinical outcomes. If different outcomes can be identified, it should add to the evidence base underlying current consensus and serve as a spur to planning further research. However, one major barrier to effective comparison lies in the fact that studies in expert centers are necessarily undertaken in populations that are selected by referral. It follows that the results of comparison are only meaningful when the populations (of both people and ulcers) are well characterized. This is the rationale for the drive to develop simple but robust classifications, as has been argued elsewhere (1). Nevertheless, there is one group of foot ulcers in which case definition is less problematic—the neuropathic ulcer, whether on the plantar surface of the foot or elsewhere. The classic neuropathic ulcer is readily recognized in clinical practice, being associated with surrounding callus and occurring on a foot with loss of protective sensation but relative preservation of peripheral arterial blood supply. The relative homogeneity of the ulcer type means that much of the influence of selective referral on the population may be negated, and comparison of outcomes between centers is potentially more meaningful.

There are a number of published studies summarizing observed healing time of neuropathic ulcers, although most of these have been concerned with the healing of ulcers on the sole of the foot. The reported rates of healing—usually defined as percent healed by 12 weeks, 20 weeks, 6 months, or 12 months—have varied widely. Thus, the analysis by Margolis et al. (2) of the control groups of various intervention trials reported that the weighted mean percent healed at 12 and 20 weeks was just 24.2 and 30.9%, respectively. Marston et al. (3) reported healing by 12 weeks in only 18.3% of control subjects in a multicenter study on one human skin substitute product, whereas Veves et al. (4) reported 38% healing by 12 weeks in another. These results must be contrasted with a recent study of two offloading devices in which Katz et al. (5) noted a crude 12-week healing rate of plantar neuropathic ulcers, which was as high as 80 and 74%. Margolis et al. also noted that the rate of healing of neuropathic ulcers seems to be steadily (6) improving in the U.S., and it is presumed that this is the result of an overall improvement in the quality of management and, in particular, in the provision of routine offloading. However, a number of factors may underlie any residual differences in healing rate, including the general health of the patient, integrity of the arterial supply, and residual activity and weight bearing. Most importantly, Margolis et al. (7–9) also observed that the rate of healing of neuropathic ulcers is affected by wound size, as well as by race and the duration of the ulcer at presentation. The influence of cross-sectional area has also been documented by Zimny et al. (10). However, given that most reported

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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results are derived from populations selected for research (from which those with comorbidity are more likely to have been excluded, or from those managed in particular health care systems in the U.S.), we sought to determine the rate of healing that may be achieved in a consecutive series of relatively unselected neuropathic ulcers managed at a single, but well-established, specialist center in U.K. The aim of the study was to determine an overall rate of healing that may serve as a benchmark for comparison, as well as to identify factors that may be associated with healing delay. If it is possible to identify early individuals who will do less well, more informed discussion of treatment choice might be enabled.

RESEARCH DESIGN AND METHODS

— This was an observational study of the outcome of routine care of patients managed in a well-established multidisciplinary foot care clinic. The use of this database was approved by the Nottingham University Hospitals National Health Service Trust, and it has previously been established that analysis of the effectiveness of routine care does not require approval by the local research ethics committee. Details of all patients are recorded at the time of first clinic attendance, and their foot lesions are classified according to the S(AD)SAD system, which is a classification based on subcategorization of cross-sectional area, depth, sepsis, arteriopathy, and neuropathy (11). Ulcer area was estimated simply by measuring the two greatest diameters at right angles and multiplying them as if the ulcer was rectangular. Ulcers were classified in this way as being <1, 1–3, or >3 cm^2. Site was also recorded. The use of this system allows retrospective selection of cohorts presenting with different types of foot disease. For the purpose of the present study, the population comprised all patients first seen between 1 January 2000 and 31 December 2004 who had ulcers on or below the malleoli that were associated with clinical evidence of some loss of protective sensation (complete or partial loss of perception of Neurotip), with intact peripheral arterial supply (both pedal pulses palpable), and who were free from evidence of infection of either soft tissue or bone at the time of referral. Since retrospective selection of neuropathic ulcers by use of the S(AD)SAD system in this way could allow possible contamination in cases with minor traumatic injury to the skin, such as de-roofed blisters and grazes, all patients who healed within 14 days of the date of onset were excluded.

The precise date of ulcer onset is often difficult to determine, especially for those ulcers that are long established or of which the patient was unaware. It was for this reason that a prospective decision had been taken to document ulcer onset simply by calendar month. For the purposes of calculating the ulcer duration at referral, the date of onset was taken as the 15th day of that month. For ulcers that started in the same month that they were first seen, the date of onset was taken as the 15th day of the month if they were seen after that date. For ulcers first seen in the first half of the month of onset, ulcer duration was arbitrarily taken as 7 days.

Usual clinical management for neuropathic ulcers relies on regular debridement to remove surrounding callus, combined with offloading. The principle of offloading (of both plantar and nonplantar ulcers) was to adjust footwear to ensure that continued trauma to the ulcerated area was minimized, but the method adopted had to comply with that which was both safe and acceptable to each patient. The method of choice of offloading of neuropathic ulcers on the plantar surface of the foot was the use of irremovable padded fiberglass slippers and, less frequently, with below-the-knee irremovable (total contact) casts. Patients who were judged unsafe in casts, or who refused to wear them, were managed with removable orthoses (either removable casts or padded shoes), with the aim of achieving the most effective offloading practicable.

Clinical outcome (healing, minor amputation, major amputation, death) was documented as part of routine practice. When patients were lost to follow-up (most usually because of intercurrent illness being managed by a different medical team), outcome was determined whenever possible by searching their hospital records. Secondary infection (of either soft tissue or bone) that occurred after first assessment was not routinely recorded on the register. Healing was defined as complete epithelialization without discharge, determined after local podiatry when appropriate. Date of healing was recorded with precision if known. If not known, the date used was that of the first clinic visit at which healing was defined. Patients were generally seen at intervals of 1–3 weeks.

No attempt was made to select a single index ulcer for each patient, and the outcomes studied were ulcer related as opposed to patient related (12). All analyses of ulcer-related data used appropriate nonparametric statistical methods: χ^2, Spearman ρ, and Kruskal-Wallis, using SPSS version 11. Because of the small numbers in some cells, all patients with unhealed ulcers (whether persisting unhealed or unhealed at time of amputation or death) were combined into a single group for the purpose of statistical comparison with those who had healed.

RESULTS

— During the 5-year period of recruitment, 616 patients were managed, and these patients had a total (concurrent or recurrent) of 1,861 ulcers. A total of 187 (30.4%) patients with 524 (28.2%) ulcers fulfilled the inclusion criteria of having loss of protective sensation without clinical evidence of peripheral arterial disease. Of the 187 patients, 103 (66.9%) were male. A total of 31 patients (106 ulcers) were excluded because of associated infection (either soft tissue or bone) at the time of referral. Eight ulcers (in two patients) were excluded because healing occurred within 14 days of estimated onset. Age of the included population of 154 patients (410 ulcers) was 57.4 ± 12.0 years (mean ± SD). In this population, 25 patients (16.2%) had type 1 diabetes. Duration of known diabetes was 12.8 ± 9.1 years.

The median estimated duration of the 410 neuropathic ulcers at the time of first assessment was 15 days (range 1–1,046). Data on cross-sectional area, on outcome, and on date of healing was missing for three, five and two ulcers, respectively. A total of 300 (73.7% of 407) ulcers had a cross-sectional area <1 cm^2, 75 (18.4%) were 1–3 cm^2, and 32 (7.9%) were >3 cm^2. Overall, 376 (91.7% of 405) healed without any form of amputation, and the median time to healing was 63 days (range 8–1,486) (Table 1). A total of 24 (5.9%) persisted unhealed until resolved by either amputation (major or minor) or death. Five (1.2%) persisted unhealed at the time of analysis (15 September 2006). The numbers of ulcers that healed, persisted, or were resolved by amputation/death were unrelated to ulcer site (plantar or nonplantar; $P = 0.568$, χ^2). The percentage of all ulcers healed at 12 weeks was 59.3% (of 403 for which data were available), with 37.3% persisting unhealed and 1.7% resolved by either amputation or death. The equivalent percentages for 20 and 52 weeks were

Table 1—*Eventual outcome of 405 neuropathic ulcers, of which 175 were plantar and 230 were nonplantar*

	Total
Healed without surgery	376 (91.7)
Persisting unhealed	5 (1.2)
Unhealed at death	11 (2.7)
Minor amputation	11 (2.7)
Major amputation	2 (1.2)

	Plantar	Other
Healed without surgery	161 (92.0)	215 (93.5)
Persisting unhealed	1 (0.6)	4 (1.7)
Unhealed at death/amputation	13 (7.4)	11 (4.8)

Data are *n* (%).

70.5, 24.6, and 3.2% and 86.6, 7.1, and 4.6%, respectively.

The influence of cross-sectional area on eventual healing and on the median time to healing of both plantar and nonplantar ulcers is shown in Tables 2 and 3. There was a significant relationship between cross-sectional area at the time of first assessment and rate of healing, with 96.3% of all ulcers <1 cm^2 eventually healing without any form of amputation, compared with 87.7% with ulcer area of 1–3 cm^2 and 71.9% with ulcer area >3 cm^2 ($P < 0.0001$, χ^2). There was a similarly significant direct relationship between cross-sectional area and overall time to healing in days ($P = 0.014$, Kruskal-Wallis). There was also a direct relationship between ulcer duration at first assessment and cross-sectional area ($P = 0.006$, Kruskal-Wallis), as well as a positive correlation between ulcer duration at first assessment and overall time to healing (Spearman $r = 0.104$; $P = 0.047$). Full multivariate analysis was not possible because of the small number of individuals in the unhealed/amputation/death category. When the factors with a significant association with outcome on univariate analysis were entered into a series of paired analyses, the association between outcome and both site and ulcer duration at referral and healing was lost, whereas the very strong association between outcome and cross-sectional area at referral was retained ($P < 0.001$).

CONCLUSIONS — The strength of this study lies in its near complete ascertainment of outcome of the routine management of neuropathic ulcers in a single specialist center in the U.K. Since that center is known to manage more than half of all diabetic foot ulcers in the community (58 and 64% in two recent community-based surveys, J. Burnside, W. Wells, F.L.G., W.J.J., unpublished data), the population is relatively unselected and none of those referred with neuropathic ulcers were excluded. The data were recorded prospectively as part of routine clinical practice. The main weaknesses of the study relate to the method used to overcome difficulties inherent in estimating the date of ulcer onset and hence of ulcer duration at first assessment. In addition, the median duration of ulcers at the time of first assessment was relatively short, at 15 days. This is largely explained by the fact that this study included all ulcers managed by the unit, and among these were ulcers arising in people already under frequent review for preexisting lesions, as well as recurrences in a population that is encouraged to phone for immediate assessment at the first sign of any new ulcer. The method for documenting ulcer area was also relatively imprecise, although sufficiently robust for analysis of a large cohort.

Previous reports of outcomes in neuropathic ulcers have been derived from a variety of populations, of which the majority were selected either by inclusion in prospective trials or by being managed in particular health care systems in the U.S. Margolis et al. (2) studied the weighted mean rate of healing in the control arms of 10 individual intervention trials that had been published, and they reported that only 24.2% healed by 12 weeks in four trials and 30.9% healed by 20 weeks in six trials. In a study of practice in a single health care system, the same group later reported 47% healing by 20 weeks in 27,630 patients (9). They observed more recently that the rate of healing appeared to be improving and had risen to 68% at 20 weeks (6). Marston et al. (3) reported healing in just 18.3% of control subjects and 30.0% of the intervention arm of a large multicenter trial of a human skin substitute, whereas Veves et al. (4) reported healing by 12 weeks in 38% of the control subjects and 56% of the intervention group in another. Whereas the present results compare favorably with these observations, with 59.8 and 71.0% healing by 12 and 20 weeks, respectively, it should be noted that the populations selected for these intervention studies excluded ulcers of relatively recent onset. The better healing rate reported here may relate to the relatively short duration of ulcers before their first assessment. When the analysis of the present data was confined to the 267 neuropathic ulcers that had been present for >6 weeks at presentation, only 109 (39.0%) were observed to heal by 12 weeks and 150 (56.32%) by 20 weeks. These differences emphasize the importance of careful definition of study populations before any meaningful comparison can be made between results in different centers.

Zimny et al. (13,14) reported median healing times of 77.7 and 75.9 days in two observational studies of neuropathic ulcers. In one of the two multicenter trials of human skin equivalent products, Veves et al. (4) reported median healing times of 65 and 90 days in the intervention and control arms, respectively. The median healing time observed here was rather less, at 63 days, although it should again be noted that the majority of ulcers in the present study were of relatively recent onset.

It is also apparent that our patients

Table 2—*Eventual outcome of 402 neuropathic ulcers categorized by cross-sectional area*

	<1 cm^2	1–3 cm^2	>3 cm^2
Healed without surgery	286 (96.3)	64 (87.7)	23 (71.9)
Persisting unhealed	2 (0.7)	0 (0.0)	3 (9.4)
Resolved by either amputation or death	9 (3.0)	9 (12.3)	6 (18.8)

Data are *n* (%).

Table 3—*Time (in days) to outcome of 402 neuropathic ulcers categorized by both cross-sectional area and site*

	Plantar			Non-plantar		
	<1 cm^2	1–3 cm^2	>3 cm^2	<1 cm^2	1–3 cm^2	>3 cm^2
Healed without surgery	56 (14–1,486)	84 (14–1,344)	112 (14–350)	56 (8–605)	81 (14–763)	77 (11–515)
Amputation/died unhealed	315 (134–527)	90 (14–1,212)	219 (136–540)	109.5 (33–458)	161 (125–171)	37 (18–56)
Total	56 (14–1,486)	84 (14–1,344)	196 (14–540)	56 (8–605)	84 (14–763)	66.5 (11–540)

Data are medians (range).

did less well than those in the randomized trial of conservative surgery (with ulcerectomy and removal of underlying bone) reported by Piaggesi et al. (15). Whereas the outcome in the control group of this study (79.2% healed by 6 months) was comparable with our own results, the rate of healing in the intervention group was 95.5% by 6 months. Our results also appear poor in comparison with outcomes in the small study by Katz et al. (5) of two different offloading techniques, in which the median 12-week rate of healing was very high at 74 and 80%, especially as the median ulcer duration at randomization in these patients was 68 days and median ulcer area was >1 cm^2. Although the patient population in the study by Katz et al. was younger and largely non-white, there are no other obvious reasons for the discrepancy, apart from the less uniform use of offloading devices in routine clinical practice in Nottingham. Nevertheless, we observed no difference in the rate of healing of plantar and nonplantar ulcers, and given that offloading would only be expected to be beneficial in patients with plantar ulcers, there remains a strong possibility that the differences in observed healing rates may relate to other as yet unidentified factors. In the detailed analysis by Margolis et al. (7), of factors that may contribute to healing, the only ones that emerged from logistic regression were ulcer area, ulcer duration, and the race of the patient. There was no relationship with age, A1C, and sex. These data and the unexplained differences between our results and those of Katz et al. (5) should prompt larger trials to determine the overall acceptability and effectiveness of irremovable offloading devices in unselected but carefully characterized populations, as well as to determine other factors that may be responsible for delayed healing.

Both Zimny et al. (10) and Margolis et al. (7–9) have noted a consistent relationship between ulcer area and the rate of healing, and we have confirmed this finding. Margolis et al. (8) also noted a relationship between ulcer duration at first assessment and its cross-sectional area, as well as between both ulcer duration and area and the rate of subsequent healing, and we have also confirmed this observation. The implication of there being a direct relationship between ulcer duration and ulcer area, as well as between ulcer area and healing rate, is that steps should be taken to ensure that all newly occurring neuropathic ulcers are referred for expert assessment and management as soon as possible. The longer a neuropathic ulcer is present, the larger it becomes and the longer it will take to heal. Moreover, the longer an ulcer is present, the greater the chance that it will become secondarily infected, and such infection will further compromise the outcome—especially if it involves bone.

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