Diabetic foot ulceration: Why are some patients in a "revolving door"?

Vanessa Nubé, Lynda Molyneaux, Maria Constantino, Thyra Bolton, Marg McGill, Elizabeth Chua, Stephen Twigg, Dennis Yue

Minimising recurrence is an important element of treating diabetic foot ulcers. This study undertook to define those characteristics that predict which people with a diabetic foot ulcer are more likely to suffer future re-ulceration. While previous ulceration, ischaemia and foot deformity (assessed by the need for medical grade footwear) were found to be significantly associated with ulcer recurrence, these factors only accounted for a small degree of the variance. Identification of the factors that cause ulcer recurrence is essential in reducing the morbidity associated with diabetic foot ulceration, and requires further investigation.

Diabetes-related foot ulceration is a serious complication of diabetes, affecting the quality of life of both the person with diabetes and their carer. It is also known to impose a heavy economic burden on the healthcare system; the relative cost of care for those with foot ulceration being 5.4 times that for people with diabetes but without foot ulceration (Ramsey et al, 1999). In Australia, 20% of people with diabetes are considered to be at high risk of foot ulceration (International Diabetes Institute, 2000), with this figure more than doubling for those who have had diabetes for more than 20 years (Tapp et al, 2003). The number of diabetes-related amputations in Australia is approximately 3400 per year (2004–2005) and admissions for diabetic foot disease are longer than for any other diabetic complication (Australian Institute of Health and Welfare, 2008).

A multidisciplinary foot clinic was established at the Royal Prince Alfred Hospital in Sydney, Australia, more than 20 years ago, with the aim of providing care for people with diabetes who suffer from foot ulceration, infection or acute Charcot arthropathy. Having started with a simple model comprising a podiatrist and an endocrinologist, the clinic is now staffed by healthcare professionals from a variety of disciplines, including regular on-site visits from an orthopaedic surgeon, a vascular surgeon, a pedorthist (trained in design and fabrication of footwear and foot orthoses), as well as dietitians and social workers. Once

Article points

1. In this study, the authors sort to define those characteristics that predict which people with diabetic foot ulceration will go on to suffer future re-ulceration.
2. Factors usually associated with diabetic foot ulceration, such as severe neuropathy and peripheral arterial disease, could not adequately explain ulcer recurrence in this study population.
3. This research suggests that the clinical and historical variables we can determine with relative ease do not allow confident prediction of long-term outcomes for people presenting to a foot clinic of this nature with a diabetic foot ulcer.

Key words

- Foot ulcer
- Recurrence
- Ulcer-free survival

Author details can be found at the end of this article.

Page points

1. While the proportion of people whose ulcers heal, and the rate at which this is achieved at the foot clinic is good, there appears to be a sub-population who have very little time free of foot ulceration.
2. This study looked at the rate of ulcer recurrence among people attending a multidisciplinary diabetic foot ulcer clinic, and the possible predictors of re-ulceration.
3. During treatment, and at the time of discharge, participants received foot-care education. This included how to select suitable footwear, the need for podiatry care, daily foot inspection and avoidance of common causes of foot injury.

their ulcers have healed, people are discharged and referred to a public or private podiatry clinic in their local area for routine foot care.

While the proportion of people whose ulcers heal, and the rate at which this is achieved, is good, there appears to be a sub-population treated at the foot clinic who have very little time free of foot ulceration. It has been proposed that minimising ulcer recurrence, both in terms of incidence and time taken to next ulcer, provides an alternative measure of overall treatment success to traditional end points, such as ulcer healing rate (Pound et al, 2005). Hence, the aim of this study was to determine the rate of ulcer recurrence among people attending the Royal Prince Alfred Hospital multidisciplinary diabetic foot ulcer clinic, and to examine the possible predictors of re-ulceration.

Method

Data were retrieved for all patients with a diabetic foot ulcer referred over a 3-year period (n=227), with the exception of 21 individuals who attended only a single visit or had unknown outcomes. Relevant information was prospectively entered into a purpose-built electronic database. This included various clinical parameters, past history of ulceration, amputation and the number of previous ulcers. The stage and grade of ulcers were determined according to the Texan Grading System (Armstrong, 1998). Neuropathy was defined by vibratory perception threshold (measured using a biothesiometer) and inability to feel the 10g monofilament. Ischaemia was defined by the absence of pedal pulses, or an ankle–brachial pressure index of less than 0.8. Ulcers were graded C or D, in accordance with the Texan Grading System. Data were grouped according to whether the subject had ever become ulcer free during the 3-year study period, and whether the subject had recurrent ulceration. An ulcer was considered healed if the lesion became completely epithelialised and free from exudate for more than 2 weeks.

According to the standard foot clinic protocol, ulcers were managed, as appropriate, with traditional wound care methods, systemic antibiotics, regular sharp debridement, vascular assessment and intervention, and pressure off-loading. During treatment, and at the time of discharge, participants received foot-care education. This included how to select suitable footwear, the need for podiatry care, daily foot inspection and avoidance of common causes of foot injury. Booklets containing this information were also given to participants.

Individuals identified as having significant foot deformity, or abnormal foot shape, were referred for medical grade footwear (MGF) and/or foot orthoses. In this study, an MGF referral was used as a surrogate measure of clinically significant foot deformity. People with Charcot arthropathy or partial foot amputation were automatically included in this category. Information on MGF referral was available for 196 of those included in the study group. Referrals were made directly to the supplier or, for those who were financially disadvantaged, an application for government assistance for the provision of shoes and orthoses was made.

As an indicator of adherence to treatment, clinic appointment attendance was recorded.

Statistical analysis

Data were analysed using NCSS 2004 software (NCSS, Kaysville, UT, USA). Continuous data were checked for normality and presented as mean ± standard deviation, or median and interquartile range (IQR). Data not normally distributed were transformed for analysis. ANOVA was used to compare means. Categorical data were represented as percentages. The Chi-square test was used to compare groups. A Kaplan–Meier curve was constructed to determine the time to re-ulceration. Cox regression was used to determine the independent predictors for re-ulceration. Predictors examined included age, gender, duration of diabetes, mean HbA_{1c} level, neuropathy status, ischaemic status, referral for MGF, number of missed clinic appointments, extent of ulceration using the Texan Grading System and past history of

Page points

1. There was a preponderance of males in the study group and the degree of neuropathy was severe.
2. During the 3-year study period, the foot clinic treated a total of 559 ulcers.

foot ulceration. The risk of re-ulceration was calculated using Cox regression and expressed as a hazard ratio with a 95% confidence interval (CI). Data were further stratified by these predictors and a Kaplan–Meier curve was constructed, and a log-rank test carried out, to compare the groups. Significance was accepted when $P<0.05$.

Results

Clinical characteristics of the participants are shown in *Table 1*. There was a preponderance of males in the study group (68%) and the degree of neuropathy was severe, with most unable to detect vibration at the maximum biothesiometer reading of 50 volts.

Of the 227 people referred to the foot clinic with ulceration during the 3-year study period, there was a total of 559 ulcers. The median follow-up time for the total cohort was 26.4 months (IQR 16.4–33.7), and the minimum follow-up time was 6.0 months.

Two hundred and five people (90%) healed and became ulcer free for a period of time during the study period (*Figure 1*). About half of those who healed (n=104) re-ulcerated, the rest remained ulcer free for the remainder of the study period. More participants in the recurrent-ulcer group required an amputation than those who remained ulcer free (11% versus 1%, P=0.006).

During the follow-up period, 71% of

Table 1. Study participant demographics, clinical parameters and statistics.

	Overall	Never ulcer free (n=22)	Recurrent ulcer (n=104)	No recurrent ulcer (n=101)	Statistics *F value*	*Chi-squared Z value*	*P value*
Clinical parameters†							
Age (years)	63.2±11.2	67.5±11.5	62.8±10.8	62.6±11.4	1.9		0.2
Duration of diabetes (years)	16.0±10.8	18.1±12.4	16.0±10.7	15.7±10.7	0.4		0.7
Males (%)	67.8	59.1	70.2	67.0		1.1	0.6
Type 2 diabetes (%)	88.6	86	89	89		0.1	0.9
Mean HbA_{1c} (%)	8.6±2.1	8.9±2.3	8.7±2.1	8.4±2.1	0.6		0.5
Ischaemia (%)	16.6	54.5	13.9	11.0		25.7	<0.0001
Cannot feel monofilament (%)	79.9	77.8	85.2	75.0		2.7	0.3
Past ulcer (%)	50.0	50.0	54.8	24.8		20.0	<0.0001
Past amputation (%)	28.2	40.9	29.8	23.8		2.9	0.2
Foot deformity							
Medical grade footwear required (%)		53	70	51		6.8	0.03
Ulcer characteristics‡							
Texan stage (%)							
1: Epidermis		77	89	88		2.2	0.3
2: Tendon probed		18	4	6			
3: Bone probed		5	8	6			
Type of ulcer (%)							
Neuropathic		63.6	86.5	87.9		8.7	0.01
Neuroischaemic or ischaemic		36.4	13.5	12.1			
Adherence to appointments							
Number of scheduled appointments		25 [6–63]	26 [15–44]	10 [7–16]			
Number of times attended (n)		17 [6–64]	21 [13–37]	9 [6–14]			
Median number of missed appointments (n)		3 [1–8]	4 [0–7]	1 [0–5]		10.0	0.007
Attended all appointments (%)		24	28	37		18.0	0.001

†At baseline; ‡ for all ulcers treated during the 3-year study period.

participants were ulcer free at 6 months, 59% at 12 months and 46% at 24 months (*Figure 2*). For those who healed and re-ulcerated, the median time to re-ulceration was 3.9 months (IQR 0.7–10.8).

Multivariate analysis showed that there were three significant predictors for re-ulceration: (i) past history of ulceration, (ii) ischaemia and (iii) foot deformity. These predictors caused 1.9 (95% CI 1.2–4.4), 2.2 (95% CI 1.1–4.4) and 2.1 (95% CI 1.2–3.7) fold increases, respectively, in the risk of ulcer recurrence, accounting for 4.6%, 2.3% and 4.6%, respectively, of the total variance.

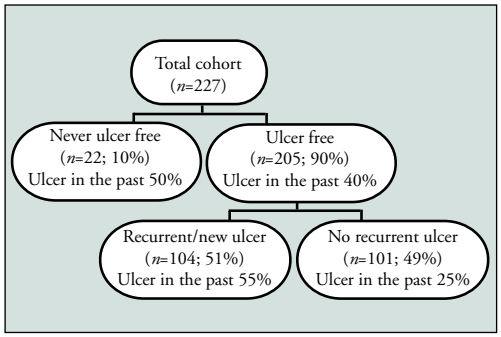

Figure 1. Participant outcomes in terms of ulcer recurrence.

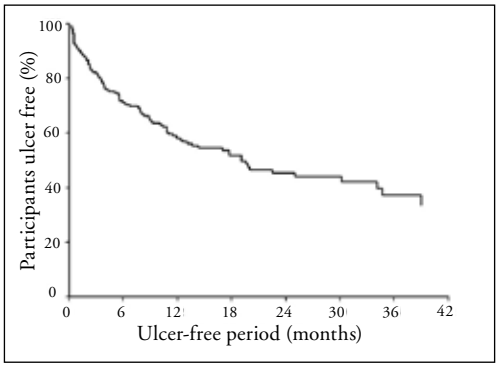

Figure 2. Time to ulcer recurrence analysed using Kaplan–Meier survival curve.

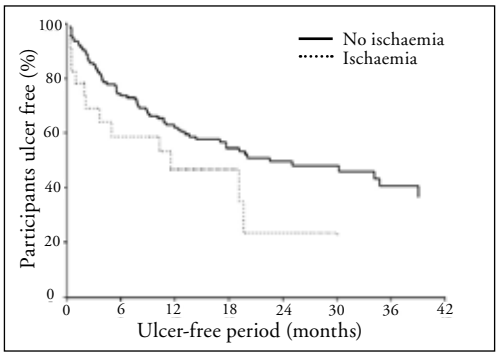

Figure 3. Time to ulcer recurrence grouped by ischaemic status using Kaplan–Meier survival curve.

When grouped by ischaemic status and analysed by Kaplan–Meier survival curve, the difference in ulcer-free period approached statistical significance (log-rank test=3.6; *P*=0.06; *Figure 3*). Seventy percent of people who experienced ulcer recurrence were referred for MGF, while fewer (51%) in the no recurrent ulcer group were deemed to require MGF.

Participants who experienced recurrent ulceration missed more foot clinic appointments than those who remained ulcer free, with a median of four versus one missed appointment, respectively. Those without ulcer recurrence were also more likely to have attended all their appointments (*Table 1*).

Twenty-two people were never ulcer free during the study period. The clinical characteristics of these people were similar to those of people whose ulcer healed at some stage (*Table 1*), except that the prevalence of peripheral arterial disease was greater (*P*<0.0001). Wounds in this group were more severe in terms of their grading for depth, though the difference was not statistically significant. Of the participants that never became ulcer free, nearly half died (*n*=10, 45%) during the study period, compared to 3% (*n*=7) among those who became ulcer free at some stage during the study (Chi-squared=50.7; *P*<0.0001).

Discussion

The Royal Prince Alfred Hospital multidisciplinary foot clinic is effective in healing ulcers in people with diabetes, but the 51% recurrence rate is disappointing. High rates of ulcer recurrence have been reported elsewhere (Apelqvist et al, 1993; Busch and Chantelau, 2003; Pound et al, 2005; Ghanassia et al, 2008) and previous studies have sought to identify the causes. Connor and Mahdi (2004) found that the presence

Page points

1. Ninety percent of the study population healed and became ulcer free for a period of time during the study.
2. The three significant predictors for re-ulceration were a past history of ulceration, ischaemia and foot deformity.
3. The clinical characteristics of those who were never ulcer free were similar to those whose ulcer healed at some stage, except that the prevalence of peripheral arterial disease was greater.

Page points

1. The factors usually associated with foot ulceration, such as severe neuropathy and peripheral arterial disease, could not adequately explain recurrence.
2. Previous foot ulceration predisposes people to re-ulceration, but the predictive value of previous ulceration is modest.
3. The clinical variables that we can determine objectively and with relative ease do not allow confident prediction of long-term outcomes for people presenting to a foot clinic of this nature.

of neuroarthropathy, poor glycaemic control, sex (preponderance of men), failure to attend clinic appointments, living alone and being non-compliant with footwear and foot care were associated with ulcer recurrence. Severity of neuropathy, poor glycaemic control, increased alcohol intake and waiting longer than 24 hours to report a foot problem have also been implicated in ulcer recurrence (Mantey et al, 1999; Jude et al, 2001). Interestingly, ischaemia was not found to be significant risk factor in these studies.

Peripheral vascular disease was shown to be a significant risk factor for recurrent foot ulceration by Peters et al (2007), who also assessed the role of ulcer location. In their study, the site of ulceration was important, with plantar hallux and plantar metatarsal ulceration recurring far more often than ulcers elsewhere. This finding did not appear to be fully explained by the higher amputation rate for ulcers on the lesser toes.

The most notable result of the current study is that factors usually associated with foot ulceration, such as severe neuropathy and peripheral arterial disease, could not adequately explain recurrence. This finding does not negate the importance of these two factors. All participants experienced severe neuropathy, but the biothesiometer measurement of neuropathy used was not sufficiently discriminating to differentiate between people with severe loss of sensation and those with even more profound sensory loss. Likewise, one of the definitions of ischaemia used was an ankle–brachial pressure index of <0.8. Using this threshold yields a categorical outcome, but does not grade the degree of tissue perfusion and therefore the extent of ischaemia. Participants with severe ischaemia may have failed to heal, and hence not been included in the analysis of ulcer recurrence.

Selection bias could also have affected the results. Individuals with more severe ischaemia may have been referred directly for surgery rather than to the foot clinic.

Unfortunately, when considered collectively, these results suggest that the clinical variables that can be determined objectively and with relative ease, by physical examination or through patient histories, do not allow confident prediction of long-term outcomes for people presenting to a foot clinic of this nature. Previous foot ulceration predisposes people to re-ulceration, but these findings indicate that the predictive value of previous ulceration is modest.

In the authors' clinical experience, foot deformity and biomechanical problems predispose people to re-ulceration. Clinical guidelines cite the importance of accommodating foot deformity with appropriate footwear (International Working Group on the Diabetic Foot, 2007) and some studies have shown that re-ulceration is reduced when MGF is worn as part of a comprehensive foot-care programme (Edmonds et al, 1986; Chantelau et al, 1990; Faglia et al, 2001; Busch and Chantelau, 2003). However, due to its pleomorphic nature, deformity is remarkably difficult to quantitate and, therefore, evidence of its importance in relation to ulceration remains in the domain of "clinical experience". Thus, in this study, significant foot deformity was defined by whether a clinical judgement had been made that MGF was necessary for a participant. These results support the notion that deformities are indeed a cause of recurrent ulceration. However, further studies, preferably with more quantitative measures, would be of great interest in this area. It is important to stress that in the context of this study, recommendation of MGF was used as a surrogate measure of significant foot deformity and no attempt has been made to correlate the actual use and appropriateness of the prescribed footwear with ultimate outcomes.

Anecdotally, the authors have observed that many people attending the foot clinic have difficulty adhering to treatment. This is, of course, the very nature of diabetic foot disease, where the absence of pain prevents the normal behavioural response to injury and illness. The data from this study showed that attendance of scheduled

clinic appointments was worse in those who experienced ulcer recurrence. Although clinic attendance may not be entirely indicative of overall concordance, modifying behaviours and improving strategies to help people with diabetic ulcers adhere to treatment may be as valuable as better clinical management in preventing re-ulceration. Judging from the small percentage of total variance explained by the factors examined here, it is axiomatic that more systematic studies are needed to explore other possible factors.

Conclusion

Studying diabetic foot ulcer recurrence has allowed us to identify the characteristics of those who experience recurrent foot ulceration over time and examine possible predictors. This study found that previous foot ulceration, ischaemia and foot deformity were associated with an increased risk of recurrent foot ulceration, but these risk factors did not explain a high degree of variance overall. Other factors, in other populations, related to re-ulceration remain to be determined by future studies. The authors concur with Pound et al (2005) that if ulcer-free survival is to be used as a measure of the effectiveness of a foot clinic, then patient population characteristics must be taken into consideration. ■

Vanessa Nubé is a Senior Podiatrist, Lynda Molyneaux is a Statistician, Maria Constantino is Database Manager and Credentialed Diabetes Educator, Thyra Bolton is a Nurse Co-ordinator, Marg McGill is the Diabetes Centre Manager and Senior Vice-President of the International Diabetes Federation, Elizabeth Chua is an Endocrinologist, Stephen Twigg is Associate Professor of Endocrinology and Dennis Yue is Professor of Endocrinology. All are based at the Royal Prince Alfred Hospital, Australia.

Apelqvist J, Larsson J, Agardh CD (1993) Long-term prognosis for diabetic patients with foot ulcers. *Journal of Internal Medicine* **6**: 485–91

Armstrong DG, Lavery LA, Harkless LB (1998) Validation of a diabetic wound classification system: The contribution of depth, infection and ischaemia to risk of amputation. *Diabetes Care* **21**: 855–9

Australian Institute of Health and Welfare (2008) *Diabetes: Australian Facts 2008*. Australian Institute of Health and Welfare, Canberra

Busch K, Chantelau E (2003) Effectiveness of a new brand of stock 'diabetic' shoes to protect against diabetic foot ulcer relapse: A prospective cohort study. *Diabetic Medicine* **20**: 665–9

Chantelau E, Kushner T, Spraul M (1990) How effective is cushioned therapeutic footwear in protecting diabetic feet? A clinical study. *Diabetic Medicine* 7: 355–9

Connor H, Mahdi OZ (2004) Repetitive ulceration in neuropathic patients. *Diabetes/Metabolism Research Reviews* **20**(Suppl 1): S23–8

Edmonds ME, Blundell MP, Morris ME et al (1986) Improved survival of the diabetic foot: The role of a specialised foot clinic. *Quarterly Journal of Medicine* **60**: 763–71

Faglia E, Favales F, Morabito A (2001) New ulceration, new major amputation, and survival rates in diabetic subjects hospitalized for foot ulceration from 1990 to 1993: A 6.5-year follow-up. *Diabetes Care* **24**: 78–83

Ghanassia E, Villon L, Thuan Dit Dieudonné JF et al (2008) Long-term outcome and disability of diabetic patients hospitalized for diabetic foot ulcers: A 6.5-year follow-up study. *Diabetes Care* **31**: 1288–92

International Diabetes Institute (2000) *Australian Diabetes, Obesity and Lifestyle Study (AusDiab).* International Diabetes Institute, Melbourne

International Working Group on the Diabetic Foot (2007) *Practical Guidelines on the Management and Prevention of the Diabetic Foot.* International Diabetes Federation, Brussels

Jude EB, Tentolouris N, Appleton I et al (2001) Role of neuropathy and plasma nitric oxide in recurrent neuropathic and neuroischemic diabetic foot ulcers. *Wound Repair and Regeneration* **9**: 353–9

Mantey I, Foster AV, Spencer S et al (1999) Why do foot ulcers recur in diabetic patients? *Diabetic Medicine* **16**: 245–9

Peters EJG, Armstrong DG, Lavery LA (2007) Risk factors for recurrent diabetic foot ulcers. *Diabetes Care* **30**: 2077–9

Pound N, Chipchase S, Treece K et al (2005) Ulcer-free survival following management of foot ulcers in diabetes. *Diabetic Medicine* **22**: 1306–9 [and comment]

Ramsey SD, Newton K, Blough D et al (1999) Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care* **22**: 382–7

Tapp RJ, Shaw JE, Decourten MP et al (2003) Foot complications in type 2 diabetes: An Australian population-based study. *Diabetic Medicine* **20**: 105–13

Page points

1. Modifying behaviours and improving strategies to help people with diabetic ulcers adhere to treatment may be as valuable as better clinical management in preventing re-ulceration.
2. Previous foot ulceration, ischaemia and foot deformity were associated with an increased risk of recurrent foot ulceration, but these risk factors did not explain a high degree of variance overall.
3. If ulcer-free survival is to be used as a measure of the effectiveness of a foot clinic, then patient population characteristics must be taken into consideration.