1 Epidemiology and Economic Impact of Foot Ulcers

Joseph W. LeMaster and Gayle E. Reiber

In the year 2005, most of the estimated 150 million people worldwide afflicted by diabetes mellitus lived in developing countries.[1] Diabetic foot ulcers will complicate the disease in more than 15% of these people during their lifetimes.[2,3] In prospective cohort studies conducted among those with diabetes, history of a foot ulcer increased the risk of subsequent amputation by two- to over three-fold.[4,5] Foot ulcers precede more than 80% of non-traumatic lower limb amputations.[6] In this chapter, we will review the definition of a 'foot ulcer' and the studies that estimate the incidence and prevalence of foot ulcers, making note of issues that need to be considered in their computation. We will also review risk factors for foot ulcers from well-conducted epidemiological studies, foot ulcer outcomes and the economic impact of foot ulcers.

FOOT ULCER DEFINITION AND CLASSIFICATION

In order to estimate accurately the occurrence of diabetic foot ulcers and risk factors associated with this diabetic complication, a common definition is needed. The International Consensus on the Diabetic Foot currently defines a diabetic foot ulcer as a full-thickness wound below the ankle in a patient with diabetes, irrespective of duration.[7] The International Working Group on the Diabetic Foot (IWGDF) also recommends that studies describing the occurrence of diabetic foot ulcers use a standard classification system to facilitate communication between health care providers, provide information about the healing potential of an ulcer and help guide management decisions. Use of such a system allows a patient to be followed up over time, allowing repeated classification of the foot ulcer. Classification systems should be sufficiently robust that intra- and inter-observer variability is low (i.e. the classification is reproducible) and should be applicable worldwide. This allows research results from one study to be compared to those of others, which is important in interpretability of results.[8] For foot ulcers, one challenge in this regard has been the numerous classification systems in existence. The most commonly used system internationally is Wagner's.[9] This system specifies ulcer depth and the presence of osteomyelitis or gangrene as a five-grade continuum:

Grade 0 Pre-ulcerative lesion

Grade 1 Partial-thickness wound up to but not through the dermis

The Foot in Diabetes, 4th Edition. Editors Andrew J.M. Boulton, Peter R. Cavanagh and Gerry Rayman.

Grade 2 Full-thickness wound extending to tendons or deeper subcutaneous tissue but without bony involvement or osteomyelitis

Grade 3 Full-thickness wound extending to and involving bone

Grade 4 Localised gangrene

Grade 5 Gangrene of the whole foot

The University of Texas system adds to this assessment four stages that specify tissue perfusion and infection: clean wounds (stage A), non-ischaemic, infected wounds (stage B), ischaemic, non-infected wounds (stage C) and ischaemic, infected wounds (stage D).[10] As discussed in Chapter 7, Dr Jeffcoate and colleagues from Nottingham developed the S(AD) SAD system, which adds to the Texas system cross-sectional area and the presence or absence of neuropathy.[11] Most recently, the IWGDF has itself developed a classification system that grades foot perfusion, wound size, depth, the presence of infection and sensation.[8] None of these systems considers the duration of the foot ulcer,[12] which may be a factor in foot ulcer treatment and time to healing.[13]

INCIDENCE AND PREVALENCE STUDIES

Reports of the incidence (new onset) and prevalence (history) of diabetic foot ulcers from many countries have begun to appear in the medical literature. To identify these studies, we conducted a literature review using the Ovid Information service, which includes Medline, the Cumulative Index to Nursing and Allied Health Literature, the Cochrane Controlled Trials register and Current Contents. We searched for articles published between January 1964 and April 2005 that used the following phrases: diabetes or diabetic, incidence, prevalence, foot ulcer, foot and feet. We also searched the bibliography of each identified article. The published studies we reviewed include population-based cohort studies, large randomised controlled trials (from which we report foot ulcer incidence among the comparison group) as well as clinic-based studies. We excluded studies that reported only lower limb ulceration (without specifying foot ulcers),[14,15] those that did not specify a foot ulcer definition of any sort[13,16,17] and studies that described a series of foot ulcer patients without clearly specifying a population base that would make it possible to estimate prevalence or incidence.[18–21]

The lifetime risk for foot ulcers in people with diabetes has been estimated to be 15%.[2] Table 1.1 shows that the annual, population-based incidence of foot ulcers among people with diabetes ranges from less than 1% to 3.6% among people with type 1 or type 2 diabetes.[16,22–30] Several methodological issues deserve consideration by those reviewing data or estimating foot ulcer incidence and prevalence in a population:

1. A number of clinic-based studies have attempted to estimate the population prevalence (and in some cases the incidence) of diabetic foot ulcers for a geographic area.[17,30,31–44] Many of these studies were well conducted and required substantial coordination across health care systems. For example, in France, a cross-sectional survey was conducted on one day in May 2001 of all patients attending outpatient clinics or admitted by 16 hospital departments that were actively involved in managing such patients.[42] Clinic-based studies make use of accessible patients. When used to measure prevalence or incidence of foot ulcers for a geographical area in community-dwelling people with diabetes, however, this

Table 1.1 Selected population-based studies estimating incidence and prevalence of diabetic foot ulcers

Study (country)	Population base	*N*	Prevalence (%)	Annual incidence[a] (%)	Ulcer definition	Ulcer ascertainment method
Rith-Najarian *et al.*[22] (United States)	Chippewa Indian residents with diabetes	266	—	0.6 (Non-neuropathic subjects)	Full thickness plantar foot lesion	Retrospective review of medical records/clinical examinations
Walters *et al.*[23] (United Kingdom)	Registered patients with diabetes from 10 UK general practices	1077	2.9 (Current) 7.4 (History of ulcer)	—	Wagner grade ≥ 1 foot lesion	Direct examination and structured interview
Moss *et al.*[16] (United States)	Population-based sample of persons with diabetes	1834	10.6 (History of ulcers at baseline)	2.2	???	Medical history questionnaire administered at baseline and 4 years later
Kumar *et al.*[24] (United Kingdom)	Type 2 diabetes patients registered in three UK cities	811	1.4 (Current) 5.3 (History of ulcer)	—	Wagner grade ≥ 1 foot lesion	Direct exam by trained observers (current), and structured interview (history of ulcer)
Abbott *et al.*[25] (United Kingdom)	Randomised controlled trial cohort	1035	—	3.6	Full-thickness lesion requiring hospital treatment	Direct examination at least every 13 weeks
Ramsey *et al.*[26] (United States)	Registered adult type 1 or 2 diabetes patients in a large HMO (1992–1995)	8905	—	1.9	ICD-codes: 707.1 (ulcer of lower leg)	Medical billing record audit
Abbott *et al.*[27] (United Kingdom)	Registered type 1 and type 2 diabetes patients in six UK districts	9710	1.7 (Current)	2.2	Wagner grade ≥ 1 foot lesion	Clinical examination (plus chart review)
Muller *et al.*[28] (Netherlands)	1993–1998 registered type 2 diabetes patients	3827 person-years	—	2.1	Full-thickness skin loss on the foot	Abstracted medical records
Centers for Disease Control and Prevention[29] (United States)	US BRFSS respondents with diabetes, 2000–2002[b]	NS	11.8 (History of ulcer)	—	Foot sore that did not heal for >4 weeks	Random-digit-dialled telephone interview

???, not specified.

[a] Incidence is annualised unless otherwise noted.

[b] BRFSS, Behavioral Risk Factor Surveillance Survey.

information may be biased because not all those with diabetes attend clinics, and those who do attend are more likely to have complications when they attend, such as diabetic foot problems. Moreover, cross-sectional surveys of clinic attendees that select a random or consecutive sample of clinic attendees are more likely to sample patients with more severe disease, because these patients attend the clinic more frequently. The preferable strategy is to sample patients from a diabetes registry that enrolls all patients in a region or a large health system.

2. Foot ulcer prevalence will also be underestimated if care is not taken to sample only patients with previously diagnosed diabetes, because a substantial proportion of patients are diagnosed with diabetes only at the time they present to clinics with a foot ulcer. In the Congolese survey cited, Monabeka and colleagues found that diabetes was first diagnosed in 2.8% of patients admitted for diabetic foot problems,[36] while in the United Kingdom, 15% of patients admitted for amputation were first diagnosed with diabetes on admission to hospital.[45] Investigators should be sure to include the foot ulcer cases for which diabetes is diagnosed at the time of foot ulcer detection in the population denominator, when calculating incidence or prevalence.

3. Wherever possible, reported foot ulcers (either by patients in surveys or by providers in clinics) should be corroborated by direct examination by investigators to avoid possible misclassification. Routine administrative or clinical billing data are subject to reporting bias, because health professionals may fail to enter the correct diagnostic code, or assign codes to maximise reimbursement. Reimbursement and administrative systems are not well suited to tracking clinical information such as ulcer episodes. Foot ulcer occurrence will be underestimated if more severe presentations (such as cellulitis or gangrene) are not counted as foot ulcers when disease in such patients started as foot ulcers. In one survey of 1654 diabetes patients hospitalised with foot problems in the Congo, only 1.2% of the cases were classified as foot ulcers, while 70.4% had either local abscess or wet gangrene.[36]

4. Prospective studies that seek to estimate ulcer incidence in a population should define a cohort of individuals who are known to be free of foot ulcers at the onset of the study, and evaluate those individuals at a later time to determine the subsequent foot ulcer presence or absence, using a clear foot ulcer definition.

5. While randomised controlled trial cohorts allow for careful ascertainment of foot ulcer incidence, they may be unsuitable to estimate incidence in the overall population of people with diabetes in the region where the study was conducted (even in controls, or in a study where the intervention was not successful and the investigators attempt to draw conclusions from the total cohort) because the sample is often highly selected, i.e. very unlike the population from which the sampled participants are drawn. In one recent clinical trial sample that was used to estimate incidence of foot ulcers, participants must have been 18–70 years old, men or non-pregnant women, had a vibration perception threshold (VPT) of $\geq$25 V on at least one foot and have had no prior foot ulceration or lower limb amputation, only diabetic causes of neuropathy, and no history of alcohol abuse, previous treatment with radiotherapy or cytotoxic agents, uncontrolled hypertension or any renal disease.[25] While these criteria are suitable to enrolls participants into a controlled trial, they make it impossible to generalise results from such a study to estimate foot ulcer incidence in the general population of people with diabetes.

Table 1.2 Anatomic site and outcome of diabetic foot lesions in two prospective studies

	All lesions[a] (%) $N = 314$	Most severe lesion[b] (%) $N = 302$
Lesion site (%)		
Toes (dorsal and plantar surface)	51	52
Metatarsal heads, midfoot and heel	28	37
Dorsum of the foot	14	11
Multiple ulcers	7	NA
Total	100	100

[a] Ref. 46 (Apelqvist *et al.*); study included consecutive patients whose lesions were characterised according to Wagner criteria from superficial non-necrotic to major gangrene.
[b] Ref. 47 (Reiber *et al.*); study patients were enrolled with a lesion through the dermis that could extend to deeper tissue.

ANATOMIC LOCATION OF FOOT ULCERS

The anatomic site of foot ulcers varies according to the population from which the patients are drawn. Table 1.2 presents data from two prospective studies that reported foot ulcer site. Those studies using patients from general diabetes clinics found that the most common ulcer sites were the toes (dorsal and plantar surface), followed by the metatarsal heads.[46,47]

US COUNTRYWIDE ESTIMATES OF FOOT-ULCER-RELATED CONDITIONS

The ability to identify foot ulcers in individuals in clinics, offices and outpatient settings is difficult, due to limited surveillance systems. However, information on patients hospitalised with foot-ulcer-related conditions is available in many countries. In the United States, for example, the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS) reports a 20% stratified sample of US community hospitals discharges (excluding discharges from Department of Veterans Affairs and military hospitals). In Table 1.3 the data for 2001 and 2002 by International Classification of Diseases (ICD-9) codes, weighted to reflect the US civilian population, show that the leading reasons for hospitalisation among diabetic patients with foot-ulcer-related conditions are cellulitis and abscess, lower limb ulcers and osteomyelitis.[48]

RISK FACTORS FOR DIABETIC FOOT ULCERS

Independent risk factors for diabetic foot ulcers were identified from analytic and experimental studies that used multivariable modelling techniques and included a defined foot ulcer outcome. Results shown in Table 1.4 demonstrate that the most consistent independent foot ulcer risk factors were long diabetes duration, measures of peripheral neuropathy and peripheral vascular disease, prior foot ulcer and prior amputation. Long duration of diabetes, even after controlling for age, was a statistically significant finding in three studies.[16,23,24] The independent role of plantar foot pressure remains unclear.

Table 1.3 Frequency of foot-ulcer-related conditions in hospitalised individuals with diabetes, 2001–2002

Type of ulcer	ICD-CM code	Estimated US frequency, 2001	Estimated US frequency, 2002
Cellulitis, abscess or infected ulcer	681.1	26 685	29 347
Other cellulitis and abscess, foot, except toes	682.7	81 367	83 954
Ulcer of lower limbs, except decubitus	707.1	209 088	216 785
Osteomyelitis	730.07	60 989	66 591
	730.17		
	730.27		
	730.37		
	730.87		
	730.97		
Chronic non-healing ulcers	707.0	129 466	134 274
	707.9		
Atherosclerosis of lower limb with ulcer or gangrene	440.23	83 546	78 983
	440.24		

Source: Nationwide Inpatient Sample, 2001, 2002.[48]

Assessment of diabetic peripheral neuropathy is performed using several semi-quantitative and quantitative measures and neurological summary scores. Associations between peripheral neuropathy and foot ulcers are uniform across the studies reported in Table 1.4. Boyko and colleagues found an increased risk of ulcers in patients who were insensate to the 5.07 (10-g) monofilament, a semi-quantitative measure of light touch.[30,50] Kastenbauer and associates found that elevated VPT $\geq$ 25 V prospectively predicted foot ulcers in a cohort of type 2 patients followed up on average for more than 3 years.[37] In a randomised clinical trial that used VPT $\geq$ 25 V as an entry criteria, Abbott and colleagues found that VPT deficits and a combined neuropathy deficit score (NDS) that include both reflexes and muscle strength measures were significant predictors of incident ulcers.[25] Several years later, the same investigators, in a cohort study of 6613 diabetes patients from six UK health care districts, found similarly that NDS score, increasingly abnormal ankle reflexes and 10-g monofilament insensitivity all independently predicted new foot ulcers.[27] Carrington and associates found that peroneal motor nerve conduction velocity was strongly associated with foot ulcer risk even after controlling for sensory neuropathy.[39] Together these studies suggest that aberrations in the various sensory modalities and the presence of motor neuropathy independently predict increased foot ulcer risk.

Peripheral vascular function can be measured as absent pulses, transcutaneous oxygen tension ($TcpO_2$) decrements and low ankle–arm index (AAI). These variables predicted foot ulcers in several of the studies in Table 1.4. Low $TcpO_2$, indicating diminished skin oxygenation, and low AAI, indicating abnormal large vessel perfusion, were independent predictors of foot ulcers in the study by Boyko *et al*.[30] In Boyko and colleagues' study, laser Doppler flowmetry did not predict foot ulcer. Kumar *et al.* defined peripheral vascular involvement as the absence of two or more foot pulses or a history of previous peripheral revascularisation.[24] They reported that this variable was a significant predictor of foot ulcers. Walters *et al*. found that an absent dorsalis pedis pulse was associated with a 6.3-fold increased risk of foot ulcer (95% CI 5.57–7.0).[23] Abbott and colleagues found that having two or less palpable pedal pulses on

Table 1.4 Risk factors for foot ulcers in patients with diabetes mellitus from the final analysis models of selected studies

Study (type of analysis)	Study design, diabetes type	Long DM duration	Neuropathy (monofilament, reflex, vibration or neurological deficit score)	Low AAI, $TcpO_2$ or absent pulses	High HbA_{1c}	Deformity	Smoking	History of ulcer	Amputation
Moss *et al.*[16] (Logistic regression)	Cohort, patients with early- and late-onset diabetes = 2990	Borderline older			+		Borderline younger		
Walters *et al.*[23] (Logistic regression)	Cohort, 10 UK general practices type 1 and 2 patients = 1077	+	+ Absent light touch + Impaired pain Perception 0 VPT	+ Absent pulses 0 Doppler			0		
Litzelman *et al.*[49] (GEE)	RCT Type 2 patients = 352	0	+ Monofilament		0	0		+	Exclusion criteria
Kumar *et al.*[24] (Logistic regression)	Cross-sectional UK general practices type 2 patients = 811	+	+ NDS	+			0	0	+
Carrington *et al.*[39] (Cox regression analysis)	Cohort, single UK diabetes clinic attendees Non-diabetes = 22 Type 1 = 83 Type 2 = 86	0	+ Motor neuropathy 0 VPT 0 Pressure sensation 0 Thermal (All were in the model simultaneously)	Exclusion criteria	0			0	Exclusion criteria

(*Continued*)

Table 1.4 (*Continued*)

Study (type of analysis)	Study design, diabetes type	Long DM duration	Neuropathy (monofilament, reflex, vibration or neurological summary score)	Low AAI, $TcpO_2$ or absent pulses	High HbA_{1c}	Deformity	Smoking	History of ulcer	Amputation
Abbott *et al.*[25] (Cox regression analysis)	RCT, patients with VPT $\geq$ 25 V (United States, United Kingdom, Canada) Type 1 = 255 Type 2 = 780	0	0 Monofilament + VPT + Reflex	Exclusion criteria				Exclusion criteria	Exclusion criteria
Boyko *et al.*[30] (Cox regression analysis)	Cohort, veterans Type 1 = 48 Type 2 = 701	0	+ Monofilament	+ AAI +$TcpO_2$	0	+ Charcot	0	+	+
Kastenbauer *et al.*[37] (Logistic regression)	Cohort Type 2 = 187	0	0 Monofilament + VPT	Exclusion criteria	0	0	0	Exclusion criteria	Exclusion criteria
Abbott *et al.*[27] (Cox regression analysis)	Cohort, United Kingdom registered diabetes patients from six UK health districts Type 1 or 2 = 6613	0	0 VPT + Monofilament + NDS + Reflex	+		+	0	+	

Blank, not studied; +, statistically significant finding; 0, no statistically significant finding; AAI, ankle–arm index; DM, diabetes mellitus; $HbA_{1c,}$ haemoglobin A_{1c}; RCT, randomised controlled trial; $TcpO_2$, transcutaneous oxygen tension; VPT, vibration perception threshold; NDS, neuropathy disability score.

both feet (at the dorsalis pedis or posterior tibial arteries) predicted increased foot ulcer risk, after controlling for neuropathy measures, history of prior foot ulcer and foot deformity.[27]

The proportion of foot ulcers with both neuropathy and ischaemia is fairly consistent internationally. In the United Kingdom, Kumar *et al*. found neuropathy alone in 46% of those with a history of foot ulcer, ischaemia alone in 12%, neuropathy and ischaemia (neuroischaemia) in 30% and neither in 12%.[24] Similarly, Walters *et al.*, also working in the United Kingdom, and Nyamu *et al.* in a carefully conducted clinic-based study in Kenya found that the greatest proportion of foot ulcers were neuropathic, followed by neuroischaemic and lastly by ischaemic ulcers, and that ischaemia was present in about half the ulcers overall.[23,40] On the other hand, the proportion of foot ulcers that are ischaemic is less in some lesser developed countries, compared to more developed countries. Morbach *et al.*, in a study comparing foot ulcers classified by the Wagner system across several countries, found that peripheral vascular disease was present in 48% of foot ulcers in Germany, but in only 11% of ulcers in Tanzania and 10% in India.[51]

The risk associated with a prior history of ulcers was assessed in five studies. Boyko *et al.*, Litzelman *et al.* and Abbott *et al.* reported that a prior history of foot ulcers significantly increased the likelihood of a subsequent ulcer.[27,30,49] Kumar *et al.* reported a relationship between prior amputation and subsequent ulcer.[24] Rith-Najarian and colleagues (though they did not use a multivariate approach and hence their study is not shown in Table 1.4) found an incidence rate of foot ulcers of 6/1000 person-years at risk among people with diabetes who had no history of prior foot ulcer, intact foot sensation and no foot deformity, whereas the rate was 330/1000 person-years at risk if all three of these criteria were present.[22]

Health care access and availability of diabetes education have been reported to influence development of foot ulcers. In a randomised trial conducted by Litzelman *et al.* in a county hospital population, diabetes patients were randomised to education, behavioural contracts and reminders, while concurrently their providers received special education and chart prompts. The control population in this study received usual care and education. After 1 year, patients in the intervention group reported more appropriate foot self-care behaviours, including inspection of feet and shoes, washing of feet and drying between toes. Not all desirable behaviours were adopted. There was no significant difference between patient groups in testing of bath water temperature and reporting of foot problems. Patients in the intervention group developed fewer serious foot lesions including ulcers than did those in the control group.[49] Among the five studies reported in Table 1.4 that included glycosylated haemoglobin (HbA_{1c}, indicating medium-term glycaemic control) in their analyses,[16,30,37,39,49] only HbA_{1c} or blood glucose levels was positively associated and foot ulcers: Moss *et al.* found a statistically significant association between increasingly poor HbA_{1c} and subsequent foot ulcers in their cohort study, with an odds ratio of 1.6 (95% CI l.3–2.0) for every 2% deterioration in this measure.[16]

The relationship between smoking and foot ulcers was assessed in six studies reported in Table 1.4;[23,24,27,30,37,39] however, it was only of borderline significance in the younger population in the Wisconsin study.[16] Moss and colleagues found that current smokers younger than 30 years were more likely to ulcerate, with odds ratio 2.3 (95% CI 1.0–5.6).[16] Kastenbauer and colleagues found that daily intake of alcohol also increased ulcer risk.[37] The cohort study by Boyko *et al.* also identified higher body weight, insulin use and history of poor vision as three additional independent predictors of foot ulcer.[30]

Four of the studies reported in Table 1.4 address the relationship between deformity and subsequent foot ulcer.[27,30,37,49] The study by Boyko *et al.* found an independent association between Charcot deformity and foot ulcer, but other foot deformities were not independent ulcer

predictors.[30] Foot deformity did not enter the final analytic model in the studies by Litzelman *et al.*[49] or Kastenbauer *et al.*[37] A number of other studies not presented in Table 1.4 have assessed the role of elevated foot pressure in foot ulcer development, using case–control comparisons. As long ago as 1963, Bauman and Brand found elevated plantar pressures under the feet of people with neuropathic insensitivity, foot deformities and foot ulcers.[52] Mueller and colleagues found that patients with diabetes and a history of foot ulcers had significantly reduced ankle dorsiflexion and subtalar joint range of motion, compared to those without diabetes.[53] In a similar study, Zimny *et al*. found that those with diabetic neuropathy but no history of foot ulcers also had reduced dorsiflexion and subtalar motion, compared to non-diabetic controls.[54] Recently, Robertson *et al.* found, using spiral computerised tomography, that plantar tissue muscle density was decreased and that metatarso-phalangeal arthropathy (especially hammer toe deformity) was more likely to be present in those with diabetic peripheral neuropathy and a history of plantar ulcer than in normal controls ($P < 0.001$).[55] In another study by the same group, Mueller *et al.* found that peak plantar pressure during walking was significantly greater in those who had both diabetic peripheral neuropathy and hammer toes than in normal controls.[56] Van Schie *et al.* found a greater frequency of both foot deformities (hammer toes, claw toes, prominent metatarsal heads and high medial arch) and foot muscle weakness (in both intrinsic and extrinsic muscles) ($P < 0.001$, Kruskal–Wallis test for trend in both types of comparisons) in those with a history of diabetic foot ulcers than in diabetic, non-neuropathic and non-diabetic controls.[57]

In reports from prospective cohort studies, progressively higher plantar pressure predicts increasing foot ulcer risk.[35,58] Despite these associations, prospective studies have been unable to demonstrate an optimal cut-point for increasing plantar pressure, above which the probability of foot ulceration is substantially increased.[43,59] This may be the case because other factors, such as weight-bearing activity, act together with plantar pressure to increase foot ulcer risk. Maluf and Mueller in a case–control study found that cumulative plantar tissue stress (which they defined as the combination of plantar pressure and total daily weight-bearing activity) was *reduced* in those with a history of diabetic neuropathic ulcers compared to either those with neuropathy alone or non-diabetic controls ($P = 0.03$).[60] The authors speculated that plantar tissues in those who ulcerated may have been more vulnerable to ulceration due to disuse atrophy. That study measured plantar pressure once at study onset, and measured weight-bearing activity over the ensuing week. Ledoux *et al.* investigated the relationship between ulcer location and peak plantar pressure at one Veterans Affairs (VA) medical centre in 549 individuals with diabetes, each of whom had in-shoe plantar pressure measured using the F-scan plantar pressure measurement device. After an average of 2.5 years of follow-up, there were 42 patients who developed plantar ulcers. In an analysis that considered whether plantar pressure differed within each foot site by foot ulcer occurrence, no significant difference was seen for peak pressure. Sites at which ulcers developed had higher mean pressure than other sites, but the site of highest pressure was unrelated to the foot ulcer site.[61] Together, these studies represent a substantial shift over time in our understanding of the role of plantar pressure and foot ulceration. It is becoming clear that while foot deformities and associated plantar pressure are important risk factors for diabetic foot ulcer, other as yet unidentified factors probably play an important synergistic role with plantar pressure in the development of foot ulcers. Further prospective studies are needed to investigate the joint role of plantar pressure and weight-bearing activity using technology that measures cumulative plantar tissue stress continuously, via an in-shoe system. Such systems are being developed[62] and will greatly improve investigation in this area.

ULCER OUTCOMES

Table 1.5 shows the outcomes of incident ulcers reported from three prospective studies of foot ulcers. The proportion of patients with diabetic foot ulcer who progress to at least partial amputation ranges from 11 to 24%, depending on ulcer severity and length of follow-up.[26,28,46,47,63] Factors associated with amputation once foot ulcer occurs will be reviewed in the next chapter. Later chapters will review therapeutic strategies for treatment of diabetic foot ulcer; however, a number of studies have found that, given similar care, ulcer surface area and ulcer duration prior to the start of treatment delay ulcer healing.[13,63–66] In a study of 194 ulcers that were re-examined weekly for 6–18 months, Oyibo and colleagues found that ulcer surface area differed strongly and significantly between ulcers that healed, did not heal or proceeded to amputation (larger ulcers having worse outcomes and taking longer to heal). Patient gender, age and duration of diabetes at presentation, and site of the ulcer on the foot did not affect time to healing. Neuroischaemic ulcers took longer to heal (20 vs 9 weeks) and were three times more likely to lead to amputation.[63] Margolis and colleagues found, after pooling data from the control arms of five related randomised studies investigating new ulcer-healing therapies, that neuropathic wounds were more likely to heal within 20 weeks if they were smaller (<2 cm^2), had existed for a shorter period before they were treated (<6 months) or if the patients were of non-White ethnicity.[13] Gender, age and glycosylated haemoglobin level had no effect in their multivariable regression model. In an analysis that utilised medical records from 150 wound care facilities in 38 US states, these same investigators confirmed that among 72 525 diabetic foot wounds in 31 106 patients, wounds that were older, larger and deeper in grade (especially Wagner grade ≥ 3) were more likely to take more than 20 weeks to heal, after adjustment for gender and age.[64] Pecoraro and colleagues described the importance of a 4-week reduction in ulcer volume and reported that low levels of periwound $TcpO_2$ and CO_2 were significantly associated with initial rate of healing, while an average periwound $TcpO_2$ <20 mm Hg was associated with a 39-fold increased risk of early healing failure.[66] Sheehan and colleagues similarly found, among 276 patients with Wagner grade ≥ 1 diabetic foot ulcers of 30 days duration, that change in ulcer area within 4 weeks of treatment onset strongly predicted complete wound healing by 12 weeks.[65] All patients in each of these studies received similar ulcer care, which included offloading, wound debridement and moist wound dressings.[13,63–65]

Foot ulcer recurrences were addressed in a UK study by Mantey and colleagues.[67] Diabetic patients with an initial foot ulcer and two ulcer recurrences were compared with diabetic patients who had only one ulcer and no recurrences over a 2-year interval. The authors reported greater peripheral sensory neuropathy and poor diabetes control in the ulcer recurrence group. Members of the ulcer recurrence group had higher glycosylated haemoglobin levels, waited longer after observing a serious foot problem until seeking care and consumed more alcohol than did the group without ulcer recurrences. Several years later, Connor and Mahdi reported on their cohort analysis of 83 patients followed up for 2–10 years after their initial foot ulcer.[68] They found that the 37% of patients with a higher rate of recurrence ($\geq$3.5 ulcers per foot per 10 years) accounted for 68% of all inpatient days and 75% of all amputations. These patients fell into two distinct groups: those with neuroarthropathy, who were more likely to wear non-orthotic footwear and had problems with footwear or orthoses, and those without neuroarthropathy, who attended clinic irregularly. Both groups had poorer glycaemic control than those with less ulcer recurrence.

Table 1.5 Frequency of lesion outcomes for diabetic foot ulcers in three prospective studies

	All lesions followed until final outcome[a]	All lesions followed for 6–18 months[b]	Most severe lesion followed until final outcome[c]
Number of ulcers	314	194	302
Re-epithelialisation/primary healing (%)	63	65	81
Amputation at any level (%)	24	15	14
Remained unhealed (%)	0	16	0
Death (%)	13	3.5	5
Total (%)	100	100	100

[a] Ref. 46 (Apelqvist *et al.*); lesions were characterised according to Wagner criteria from superficial non-necrotic to major gangrene.

[b] Ref. 63 (Oyibo *et al.*); lesions were grade 1 or deeper in the S(AD) SAD foot ulcer classification system.

[c] Ref. 47 (Reiber *et al.*); study patients were enrolled with a lesion through the dermis that could extend to deeper tissue.

ECONOMIC CONSIDERATIONS FOR FOOT ULCERS

Studies on foot-ulcer-related conditions usually report only direct patient costs or charges such as outpatient visits, procedures, pharmaceuticals and hospitalisations, since indirect costs (value of lost income from work, pain, suffering and family burden) are difficult to measure. Two studies assessed the economic impact of ulcers and amputations, and followed the lesion from the onset of the ulcer episode to each lesion's final resolution. Ramsey conducted a nested case–control study in a large health maintenance organisation (HMO) that involved 8905 patients with diabetes. Of this group, 514 individuals developed one or more foot ulcers, and 11% of these patients required amputation. Costs were computed for the year prior to the ulcer and the two years following the ulcer, for both cases and controls. The excess cost attributed to foot ulcers and their sequelae averaged $27 987 per patient for the 2-year period following ulcer presentation.[26] Apelqvist followed 314 patients across their ulcer episode, and reported healing was achieved in $\leq$2 months in 54% of patients, in 3–4 months in 19% of patients and in $\geq$5 months in 27% of patients. There were 63% of patients who healed without surgery at an average cost of $6664. Lower limb amputation was required for 24% of patients at an average cost of $44 790. The 13% of patients who died prior to final ulcer resolution were excluded from this analysis. The proportion of all costs that were related to hospitalisation was 39% among ulcer patients and 82% among amputees.[69]

Direct costs for US patients with private insurance are available from the Medstat group, who manages a large US integrated administrative claims system affiliated with private health insurance plans. Table 1.6 shows reimbursement to hospitals for patients with selected foot conditions by Diagnostic Related Group (DRG). For example, for DRG 271, i.e. skin ulcers, patients with private insurance averaged 11-day hospitalisation at a cost of $11 638, while those whose coverage was Medicare had an average 7.3-day length of stay and an average

Table 1.6 Reimbursement to hospitals for patients with and without diabetes, 2002

		Medstat (private)		Medicare	
DRG	Condition	LOS	Average reimbursement (in $)	LOS	Average reimbursement (in $)
277	Cellulitis, age >17 with complications	4.8	6 823	5.7	4 000
278	Cellulitis, age >17 without complications	3.4	4, 426	4.2	2 192
271	Skin ulcers	11.0	11 638	7.3	5 227
238	Osteomyelitis	5.9	9 913	8.7	7 376

Source: Medstat group, Thompson Corporation, 2005[70]; Centers for Medicare and Medicaid Services, 2005[71]. DRG, Diagnostic Related Group; LOS, length of stay.

hospital reimbursement of $5227 according to the Centers for Medicare and Medicaid Services. Payment for the health care providers is not included in these figures.[70,71]

In summary, foot ulcer prevalence and incidence is increasing globally and is challenging to measure, due to a lack of outpatient- and clinic-based surveillance systems. Peripheral neuropathy and its sequelae, a long duration of diabetes and peripheral vascular disease are the most consistent risk factors for predicting a foot ulcer. Re-ulceration occurs in about 60% of persons with prior ulcers and is more common among those with more severe peripheral neuropathy, increased alcohol consumption, poorer blood glucose control and delays in seeking ulcer care. Costs are high to the patient and the health care system.

REFERENCES

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414–1431.
2. Palumbo PJ, Melton LJ III. Peripheral vascular disease and diabetes. In: National Diabetes Data Group (US), National Institute of Diabetes and Digestive and Kidney Diseases (United States), eds. *Diabetes in America.* Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:401–408.
3. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA* 2005;293:217–228.
4. Adler AI, Boyko EJ, Ahroni JH, *et al*. Lower-extremity amputation in diabetes. The independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. *Diabetes Care* 1999;22:1029–1035.
5. Moss SE, Klein R, Klein BE. The 14-year incidence of lower-extremity amputations in a diabetic population. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care* 1999;22:951–959.
6. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. *Diabetes Care* 1990;13:513–521.
7. Apelqvist J, Bakker K, van Houtum WH, *et al. International Consensus on the Diabetic Foot.* Maastricht, the Netherlands: International Working Group on the Diabetic Foot; 1999.
8. Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. *Diabetes Metab Res Rev* 2004;20:S90–S95.

9. Wagner FW Jr. The dysvascular foot: a system for diagnosis and treatment. *Foot Ankle* 1981;2:64–122.
10. Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. *J Foot Ankle Surg* 1996;35:528–531.
11. Treece K, Macfarlane R, Pound N, *et al.* Validation of a new system of foot ulcer classification in diabetes mellitus. Nottingham, UK: Department of Diabetes and Endocrinology, City Hospital; 2005.
12. Macfarlane RM, Jeffcoate WJ. Factors contributing to the presentation of diabetic foot ulcers. *Diabet Med* 1997;14:867–870.
13. Margolis DJ, Kantor J, Santanna J, *et al.* Risk factors for delayed healing of neuropathic diabetic foot ulcers: a pooled analysis. *Arch Dermatol* 2000;136:1531–1535.
14. Wong I. Measuring the incidence of lower limb ulceration in the Chinese population in Hong Kong. *J Wound Care* 2002;11:377–379.
15. Andersson E, Hansson C, Swanbeck G. Leg and foot ulcer prevalence and investigation of the peripheral arterial and venous circulation in a randomised elderly population. An epidemiological survey and clinical investigation. *Acta Derm Venereol* 1993;73:57–61.
16. Moss SE, Klein R, Klein BE. The prevalence and incidence of lower extremity amputation in a diabetic population. *Arch Intern Med* 1992;152:610–616.
17. Tseng CH. Prevalence and risk factors of diabetic foot problems in Taiwan: a cross-sectional survey of non-type 1 diabetic patients from a nationally representative sample. *Diabetes Care* 2003;26: 3351.
18. Gulam-Abbas Z, Lutale JK, Morbach S, *et al.* Clinical outcome of diabetes patients hospitalized with foot ulcers, Dar es Salaam, Tanzania. *Diabet Med* 2002;19:575–579.
19. Yalamanchi H, Yalamanchi S. Profile of diabetic foot infections in a semiurban area of a developing country. *Diabetologia* 1997;40:A468.
20. Akanji AO, Adetuyidi A. The pattern of presentation of foot lesions in Nigerian diabetic patients. *West Afr J Med* 1990;9:1–5.
21. Benotmane A, Mohammedi F, Ayad F, *et al.* Diabetic foot lesions: etiologic and prognostic factors. *Diabetes Metab* 2000;26:113–117.
22. Rith-Najarian SJ, Stolusky T, Gohdes DM. Identifying diabetic patients at high risk for lower-extremity amputation in a primary health care setting. A prospective evaluation of simple screening criteria. *Diabetes Care* 1992;15:1386–1389.
23. Walters DP, Gatling W, Mullee MA, *et al.* The distribution and severity of diabetic foot disease: a community study with comparison to a non-diabetic group. *Diabet Med* 1992;9:354–358.
24. Kumar S, Ashe HA, Parnell LN, *et al*. The prevalence of foot ulceration and its correlates in type 2 diabetic patients: a population-based study. *Diabet Med* 1994;11:480–484.
25. Abbott CA, Vileikyte L, Williamson S, *et al*. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. *Diabetes Care* 1998;21:1071–1075.
26. Ramsey SD, Newton K, Blough D, *et al*. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care* 1999;22:382–387.
27. Abbott CA, Carrington AL, Ashe H, *et al.* The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med* 2002;19:377–384.
28. Muller IS, de Grauw WJ, van Gerwen WH, *et al.* Foot ulceration and lower limb amputation in type 2 diabetic patients in Dutch primary health care. *Diabetes Care* 2002;25:570–574.
29. Centers for Disease Control and Prevention. History of foot ulcer among persons with diabetes – United States, 2000–2002. *MMWR Morb Mortal Wkly Rep* 2003;52:1098–1102.
30. Boyko EJ, Ahroni JH, Stensel V, *et al.* A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. *Diabetes Care* 1999;22:1036–1042.
31. Holewski JJ, Moss KM, Stess RM, *et al*. Prevalence of foot pathology and lower extremity complications in a diabetic outpatient clinic. *J Rehabil Res Dev* 1989;26:35–44.

32. Wikblad K, Smide B, Bergstrom A, *et al*. Outcome of clinical foot examination in relation to self-perceived health and glycaemic control in a group of urban Tanzanian diabetic patients. *Diabetes Res Clin Pract* 1997;37:185–192.
33. Nielsen JV. Peripheral neuropathy, hypertension, foot ulcers and amputations among Saudi Arabian patients with type 2 diabetes. *Diabetes Res Clin Pract* 1998;41:63–69.
34. Vijay V, Narasimham DV, Seena R, *et al.* Clinical profile of diabetic foot infections in south India – a retrospective study. *Diabet Med* 2000;17:215–218.
35. Pham H, Armstrong DG, Harvey C, *et al*. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. *Diabetes Care* 2000;23:606–611.
36. Monabeka HG, Nsakala-Kibangou N. Epidemiological and clinical aspects of the diabetic foot at the Central University Hospital of Brazzaville. *Bull Soc Pathol Exot* 2001;94:246–248.
37. Kastenbauer T, Sauseng S, Sokol G, *et al.* A prospective study of predictors for foot ulceration in type 2 diabetes. *J Am Podiatr Med Assoc* 2001;91:343–350.
38. Gulliford MC, Mahabir D. Diabetic foot disease and foot care in a Caribbean community. *Diabetes Res Clin Pract* 2002;56:35–40.
39. Carrington AL, Shaw JE, van Schie CH, *et al.* Can motor nerve conduction velocity predict foot problems in diabetic subjects over a 6-year outcome period? *Diabetes Care* 2002;25:2010–2015.
40. Nyamu PN, Otieno CF, Amayo EO, *et al.* Risk factors and prevalence of diabetic foot ulcers at Kenyatta National Hospital, Nairobi. *East Afr Med J* 2003;80:36–43.
41. Stein H, Yaacobi E, Steinberg R. The diabetic foot: update on a common clinical syndrome. *Orthopedics* 2003;26:1127–1130.
42. Malgrange D, Richard JL, Leymarie F, *et al.* Screening diabetic patients at risk for foot ulceration. A multi-centre hospital-based study in France. *Diabetes Metab* 2003;29:261–268.
43. Lavery LA, Armstrong DG, Wunderlich RP, *et al.* Predictive value of foot pressure assessment as part of a population-based diabetes disease management program. *Diabetes Care* 2003;26:1069–1073.
44. Lavery LA, Armstrong DG, Wunderlich RP, *et al.* Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. *Diabetes Care* 2003;26:1435–1438.
45. Deerochanawong C, Home PD, Alberti KG. A survey of lower limb amputation in diabetic patients. *Diabet Med* 1992;9:942–946.
46. Apelqvist J, Larsson J, Agardh CD. Long-term prognosis for diabetic patients with foot ulcers. *J Intern Med* 1993;233:485–491.
47. Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. *Am J Surg* 1998;176:5S–10S.
48. HCUP Databases. *Healthcare Cost and Utilization Project* (*HCUP*). *Nationwide Inpatient Sample.* Rockville, MD: Agency for Healthcare Research and Quality; June 2005. Available from: www.hcup-us.ahrq.gov/nisoverview.jsp. (updated 2005 Jun 20; cited 2005 Aug 14).
49. Litzelman DK, Slemenda CW, Langefeld CD, *et al.* Reduction of lower extremity clinical abnormalities in patients with non-insulin-dependent diabetes mellitus. A randomized, controlled trial. *Ann Intern Med* 1993;119:36–41.
50. McNeely MJ, Boyko EJ, Ahroni JH, *et al.* The independent contributions of diabetic neuropathy and vasculopathy in foot ulceration. How great are the risks? *Diabetes Care* 1995;18:216–219.
51. Morbach S, Lutale JK, Viswanathan V, *et al*. Regional differences in risk factors and clinical presentation of diabetic foot lesions. *Diabet Med* 2004;21:91–95.
52. Bauman JH, Girling JP, Brand PW. Plantar pressures and trophic ulceration: an evaluation of footwear. *J Bone Joint Surg Br* 1963;45B:652–673.
53. Mueller MJ, Diamond JE, Delitto A, *et al.* Insensitivity, limited joint mobility, and plantar ulcers in patients with diabetes mellitus. *Phys Ther* 1989;69:453–459.
54. Zimny S, Schatz H, Pfohl M. The role of limited joint mobility in diabetic patients with an at-risk foot. *Diabetes Care* 2004;27:942–946.

55. Robertson DD, Mueller MJ, Smith KE, *et al.* Structural changes in the forefoot of individuals with diabetes and a prior plantar ulcer. *J Bone Joint Surg Am* 2002;84A:1395–1404.
56. Mueller MJ, Hastings M, Commean PK, *et al.* Forefoot structural predictors of plantar pressures during walking in people with diabetes and peripheral neuropathy. *J Biomech* 2003;36:1009–1017.
57. van Schie CH, Vermigli C, Carrington AL, *et al.* Muscle weakness and foot deformities in diabetes: relationship to neuropathy and foot ulceration in Caucasian diabetic men. *Diabetes Care* 2004;27:1668–1673.
58. Veves A, Murray HJ, Young MJ, *et al*. The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study. *Diabetologia* 1992;35:660–663.
59. Armstrong DG, Peters EJ, Athanasiou KA, *et al.* Is there a critical level of plantar foot pressure to identify patients at risk for neuropathic foot ulceration? *J Foot Ankle Surg* 1998;37:303–307.
60. Maluf KS, Mueller MJ. Novel Award 2002. Comparison of physical activity and cumulative plantar tissue stress among subjects with and without diabetes mellitus and a history of recurrent plantar ulcers. *Clin Biomech* (*Bristol, Avon*) 2003;18:567–575.
61. Ledoux WR, Cowley MS, Ahroni JH, *et al.* No relationship between plantar pressure and diabetic foot ulcer incidence after adjustment for ulcer location. *Diabetes* 2005;54:A17.
62. Maluf KS, Morley RE Jr, Richter EJ, *et al.* Monitoring in-shoe plantar pressures, temperature, and humidity: reliability and validity of measures from a portable device. *Arch Phys Med Rehabil* 2001;82:1119–1127.
63. Oyibo SO, Jude EB, Tarawneh I, *et al.* The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diabet Med* 2001;18:133–138.
64. Margolis DJ, Allen-Taylor L, Hoffstad O, *et al.* Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. *Diabetes Care* 2002;25:1835–1839.
65. Sheehan P, Jones P, Caselli A, *et al.* Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care* 2003;26:1879–1882.
66. Pecoraro RE, Ahroni JH, Boyko EJ, *et al*. Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. *Diabetes* 1991;40:1305–1313.
67. Mantey I, Foster AV, Spencer S, *et al.* Why do foot ulcers recur in diabetic patients? *Diabet Med* 1999;16:245–249.
68. Connor H, Mahdi OZ. Repetitive ulceration in neuropathic patients. *Diabetes Metab Res Rev* 2004;20:S23–S28.
69. Apelqvist J, Ragnarson-Tennvall G, Persson U, *et al.* Diabetic foot ulcers in a multidisciplinary setting. An economic analysis of primary healing and healing with amputation. *J Intern Med* 1994;235:463–471.
70. Center for Medicare Services. *Diagnostic Related Groups Inpatient Billing Data*; 2005. Available from: www.cms.hhs.gov/statistics/medpar/DRG500_02_i.pdf. (updated 2003 Jun; cited 2005 Aug 14).
71. Medstat. *Diagnostic Related Groups Billing Data 2002.* Ann Arbor, MI: Medstat; 2005.