

Epidemiology and Health Care Costs of Diabetic Foot Problems

Gayle E. Reiber, MPH, PhD

INTRODUCTION

The frequency of nontraumatic lower limb amputations in persons with diabetes has increased in the United States over the last decade. Currently two-thirds of all lower limb amputations occur in individuals with diagnosed diabetes. High geographic variation in age, sex, and race-adjusted amputation rates across U.S. populations suggest that important differences in practice patterns exist and that some patients may be receiving suboptimal care. Amputations reduce patient function and quality of life and place a heavy burden on individuals, families, and health care systems. In this chapter the epidemiology and risk factors for two major diabetic foot problems, ulcers and lower limb amputations, are described. Foot ulcer and amputation hospital discharge data are presented from two major U.S. surveys, the Nationwide Inpatient Sample (NIS), a database that also includes utilization and charge information, and the National Hospital Discharge Survey (NHDS) (1,2). Comparisons between persons with and without diabetes are clearly specified. Findings from analytic and experimental studies that used multivariable modeling techniques to determine risk factors are presented. The chapter concludes with information on the economic impact of diabetic foot problems.

EPIDEMIOLOGY OF FOOT ULCERS

Foot ulcers result from various etiologic factors and are characterized by an inability to self-repair in a timely and orderly manner (3). The 1997 U.S. NIS indicated that 3.2% of the hospital discharges in persons with diabetes were for chronic lower limb ulcers (1).

Wide variation has been reported in incidence (new onset) and prevalence (history) of diabetic foot ulcers. Table 1 shows that the annual, population-based incidence of diabetic foot ulcers in different populations ranges from 1.0 to 4.1%, and the prevalence of foot ulcers ranges from 5.3 to 10.5% (4–8). The lifetime risk for foot ulcers in persons with diabetes is estimated at 15% (9).

The anatomic location of a foot lesion has both etiologic and treatment implications. Table 2 presents data from two large prospective studies showing that the most common ulcer sites were the toes (dorsal or plantar surface), followed by the plantar metatarsal heads (10,11). The authors caution that ulcer severity is more important than

Table 1
Population-Based Diabetic Foot Ulcer Incidence and Prevalence from Select Studies

Author	Population studied	Annual incidence/100	Prevalence/100
Borssen et al. (4)	375 patients, Umea County, Sweden; age 15–50 yr; type 1 = 298, type 2 = 77	2.0	10.0 IDDM 9.0 NIDDM
Kumar et al. (5)	Cross-sectional study of 811 type 2 patients from three UK cities	1.0	5.3
Moss et al. (6)	Cohort of 2990 patients with late- and early-onset diabetes	2.4 younger 2.6 older	9.5 younger 10.5 older
Ramsey et al. (7)	Nested case-control study in HMO, 8905 type 1, type 2	1.9	—
Walters et al. (8)	Cross-sectional study of 1077 type 1, 2 patients in 10 UK general medicine practices	4.1	7.4

Table 2
Anatomic Site and Outcome of Diabetic Foot Lesions in Two Prospective Studies

	All lesions (%) <i>n</i> = 314; Apelqvist et al. (46) ^a	Most severe lesion (%) <i>n</i> = 302; Reiber et al. (11) ^b
Lesion site, %		
Toes (dorsal and plantar surface)	51	52
Plantar metatarsal heads, midfoot and heel	28	37
Dorsum of foot	14	11
Multiple ulcers	7	NA
Total	100	100
Lesion outcomes, %		
Reepithelialization/primary healing	63	81
Amputation at any level	24	14
Death	13 ^c	5
Total	100	100

^aStudy included consecutive patients whose lesions were characterized according to Wagner criteria from superficial nonnecrotic to major gangrene.

^bStudy patients were enrolled with a lesion through the dermis that could extend to deeper tissue.

^cIncludes eight amputees who had not yet met the 6-month healing criteria.

ulcer site in determining the final outcome (10). Although foot ulcers healed in most of these patients, amputations occurred in 14% of the U.S. and 24% of the Swedish patients. The deaths in these study subjects were unrelated to the foot ulcer and were attributed to other comorbidity.

Diabetic foot ulcer conditions in the U.S. NIS include chronic ulcers, superficial and deep infections of the foot, and osteomyelitis. Figure 1 shows more foot ulcer hospital discharges in persons without diabetes than in those with diabetes. Even though there are approx 100,000 fewer hospital discharges annually in persons with diabetes, this group represents only about 5% of the U.S. population. Figure 2 shows the trend in hospital

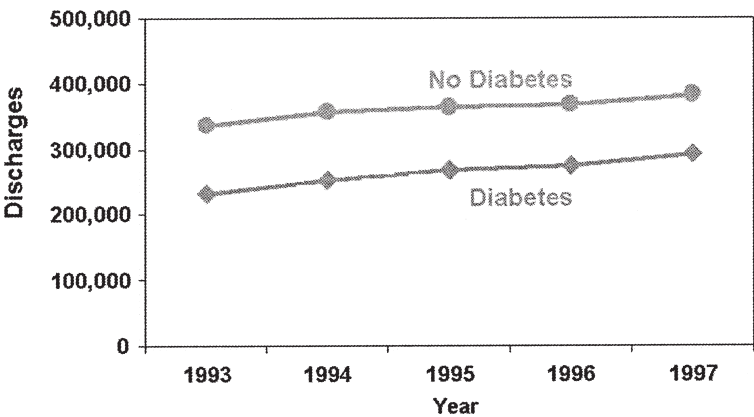


Fig. 1. U.S. hospital discharges for foot ulcers, 1993–1997. Source: Nationwide Inpatient Sample (1).

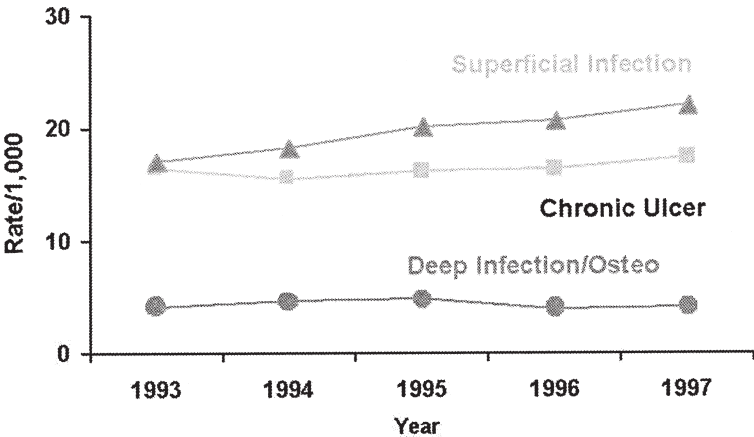


Fig. 2. U.S. hospital discharge rate/1000 for diabetic foot ulcers by condition, 1993–1997. Source: Nationwide Inpatient Sample (1).

discharges for people with diabetes for the specified ulcer conditions. Increases were noted in superficial infections and chronic ulcers, whereas deep infections and osteomyelitis remained relatively constant over the interval. Figure 3 shows that NIS hospital discharge rates rose consistently from the youngest age group to the oldest age group. The second national data source, the NHDS, documented higher hospital ulcer discharge rates in males than females and year to year variation in discharges in rates for white and nonwhite individuals, with neither group consistently higher (12).

Independent risk factors for diabetic foot ulcers from analytic and experimental studies using multivariable modeling techniques were identified. Results, summarized in Table 3, show that the most consistent independent foot ulcer risk factors were long diabetes duration, measures of peripheral neuropathy, measures of peripheral vascular disease, prior foot ulcer, and prior amputation. Long duration of diabetes, even after controlling for age, was a statistically significant finding in several studies (5,8,13). In the study by Rith-Najarian et al. (13), long duration of diabetes increased the risk of

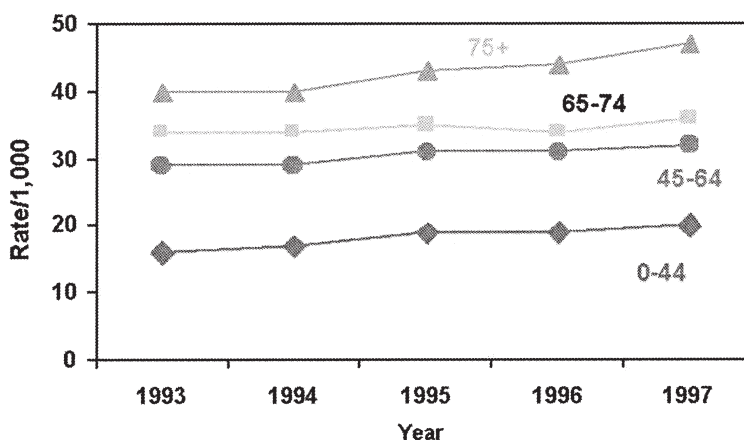


Fig. 3. U.S. hospital discharge rate/1000 for foot ulcers in people with diabetes by age, 1993–1997. Source: Nationwide Inpatient Sample (1).

foot ulcers sixfold when persons with a diabetes duration of ≤ 9 years were compared with those with a duration of ≥ 20 years (13).

Assessment of peripheral neuropathy is performed using several semiquantitative and quantitative measures and neurologic summary scores. Associations between peripheral neuropathy and foot ulcers are uniform across the studies reported in Table 3. In a randomized clinical trial using vibration perception threshold (VPT) ≥ 25 as an entry criteria, Abbott and colleagues (14) identified both baseline VPT and a combined score of reflexes and muscle strength as significant predictors of incident ulcers. Studies by Boyko et al. (15) and Rith-Najarian et al. (13) identified increased ulcer risk in patients unable to detect the 5.07 monofilament, a semiquantitative measure of light touch. There was no statistically significant association with ulcer risk in three other studies (8,14,16).

Peripheral vascular function was measured as absent pulses, transcutaneous oxygen tension ($TcPO_2$), and low ankle-arm index (AAI). These variables appeared in the final ulcer prediction model in several studies. Low $TcPO_2$ indicating diminished skin oxygenation, and low ankle-arm index AAI, suggesting impaired large vessel perfusion, were both independent predictors of foot ulcers in the study by Boyko et al. (15). However, in this study, laser Doppler flowmetry did not predictor foot ulcer. Kumar et al. (5) defined peripheral vascular involvement as the absence of two or more foot pulses or a history of previous peripheral revascularization. They reported that this variable was a significant predictor of foot ulcers. Walters et al. (8) 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).

Only one of three studies measuring HbA_{1c} or blood glucose reported an association with foot ulcers. A cohort study by Moss et al. (6), identified a statistically significant association between high levels of HbA_{1c} and subsequent foot ulcers, odds ratio 1.6 (95% CI 1.3–2.0). Three of the studies reported in Table 3 address the relationship between foot deformity and subsequent foot ulcer. The study by Boyko et al. (15) found an independent association between Charcot deformity and foot ulcer, but other foot deformities were not independent ulcer predictors. Foot deformity did not enter the final analytic model in the studies by Litzelman et al. (17) and Rith-Najarian et al. (13).

Table 3
Risk Factors for Foot Ulcers in Patients with Diabetes Mellitus from the Final Analysis Models of Select Studies

Author and type of analysis	Study design, diabetes type	Long DM duration	Neuropathy (monofilament, reflex, vibration, or neurologic summary score)	Low AAI, TcPO ₂ or absent pulses	History		
					Deformity	Smoking	Ulcer
				Exclusion criteria			Exclusion criteria
							Amputation
Abbott et al. (14) Cox regression analysis	RCT, patients with VPT ≥ 25; (US, UK, Canada), type 1 = 255, type 2 = 780	0	0 Monofilament, + VPT + Reflex	Exclusion criteria			
Boyko et al. (15) Cox regression analysis	Cohort, veterans, type 1 = 48, type 2 = 701	0	+ Monofilament	+ AAI +TcPO ₂	+ Charcot	0	+ +
Kumar et al. (5) Logistic regression	Cross-sectional, 811 type 2 from UK, general practices	+	+ NDS	+		0	0 +
Litzelman et al. (17) GEE	RTC, 352 type 2 patients	0	+ Monofilament				Exclusion criteria
Moss et al. (6) Logistic regression	Cohort, 2990 patients with early- and late-onset diabetes	Borderline older				Borderline older	
Pham et al. (16) Logistic regression	Cohort, 248 patients at three sites	Control variable	+ NDS + VPT + monofilament 0	Control variable			
Rith-Najarian et al. (13) Chi-square analysis	Cohort, 358 type 2 Chippewa Indians	+	+ Monofilament		0		
Walters et al. (8) Logistic regression	Cohort, 10 UK general practices, 1077 types 1, 2	+	+ Absent light touch + Impaired pain, perception 0 VPT	+ Absent pulses 0 Doppler		0	
blank, not studied;							
+, statistically significant finding;							
0, no statistically significant finding.							
GEE, generalized estimating equations							
				AAI, ankle arm index; DM, diabetes; HbA _{1c} , hemoglobin A _{1c} ; NDS, neuropathy disability score;	RCT, randomized controlled trial; TcPO ₂ , transcutaneous oxygen tension; VPT, vibration perception threshold;		

The relationship between smoking and foot ulcers was assessed in four studies reported in Table 3; however, it was only of borderline significance in the younger population in the Wisconsin study (6). The risk associated with a prior history of ulcers and amputations was assessed in three studies. Boyko et al. (15) and Litzelman et al. (17) reported that a prior history of ulcers significantly increased the likelihood of a subsequent ulcer. Kumar et al. (5) reported a relationship between prior amputation and subsequent ulcer. The cohort study of Boyko et al. (15) also identified higher body weight, insulin use, and history of poor vision as three additional independent predictors of foot ulcer.

Health care access and availability of diabetes education has been reported to influence development of foot ulcers. In the Litzelman et al. (17) randomized trial of a county hospital population, intervention patients were allocated to education, behavioral contracts, and reminders, while concurrently their providers received special education and chart prompts. The control population received usual care and education. After 1 year, patients in the intervention group reported more appropriate foot self-care behaviors, including inspection of feet and shoes, washing of feet, and drying between toes. Not all desirable behaviors were adopted. There was no significant difference between patient groups in testing bath water temperature and reporting foot problems. Patients in the intervention group developed fewer serious foot lesions including ulcers than did those in the control group (17).

Foot ulcer recurrences were addressed in a U.K. study by Mantey and colleagues (18). 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 waited longer after observing a serious foot problem until seeking care and consumed more alcohol than did the group without ulcer recurrences (18).

In summary, foot ulcer frequency and rates increased in the United States between 1993 and 1997. 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. Reulceration occurred in about 60% of persons with prior ulcers and was more common accompanying severe peripheral neuropathy, high alcohol consumption, poor blood glucose control, and delays in seeking ulcer care.

EPIDEMIOLOGY OF LOWER LIMB AMPUTATION

The frequency of discharges for nontraumatic lower limb amputations in persons with and without diabetes according to the 1993–1997 NIS is shown in Figure 4. The combined NIS and Veterans Health Administration hospital discharges for persons with and without diabetes are presented in Table 4. In total, of the 134,677 discharges for nontraumatic lower extremity amputations in the United States in 1997, two-thirds were performed in persons with diabetes. Only 47% of amputations in persons with diabetes were major amputations (transtibial and transfemoral) compared with 70% in persons without diabetes. This suggests that amputations performed for vascular indications in persons without diabetes were performed at higher, more disabling levels. Figure 5 illustrates the frequency of lower limb amputation by level in persons with diabetes and

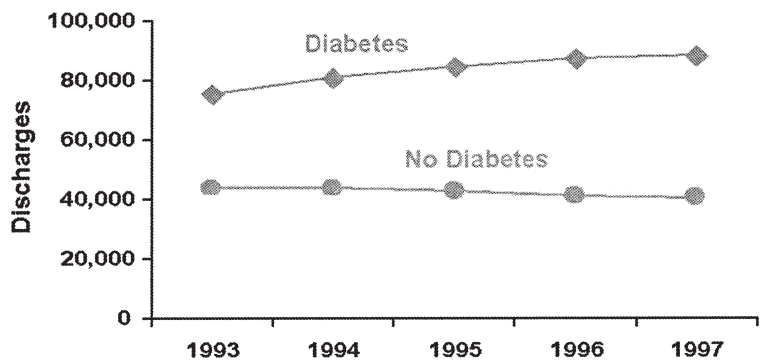


Fig. 4. U.S. hospital discharges for nontraumatic lower limb amputations, 1993–1997. Source: Nationwide Inpatient Sample (1).

Table 4
Number and Percent of U.S. Amputation Discharges
by Diabetes Status and Amputation Level, 1997

	Nationwide Inpatient Survey	VA	Total	Percent
Diabetes				
Minor amputations	46,680	1987	48,667	53
Major amputations	41,661	1678	43,339	47
Subtotal	(88,341)	(3665)	(92,006)	(68)
No Diabetes				
Minor amputations	12,128	574	12,702	30
Major amputations	28,574	1405	29,979	70
Subtotal	(40,702)	(1997)	(42,681)	(32)
Total	129,043	5644	134,687	100

U.S. nationwide inpatient sample (1); Veterans Health Administration Patient Treatment File (61).

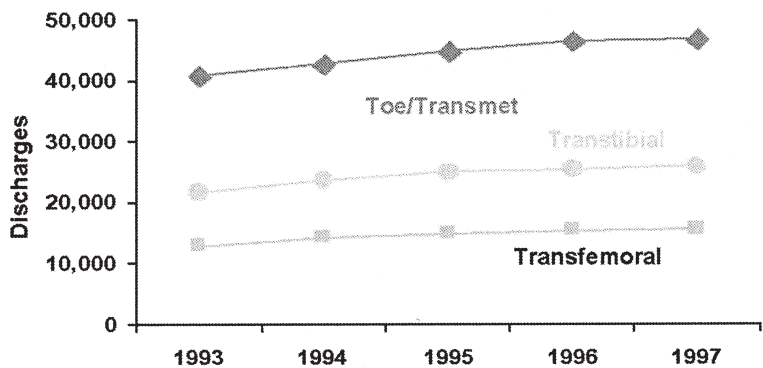


Fig. 5. U.S. hospital discharges for nontraumatic lower limb amputation by level for persons with diabetes, 1993–1997. Source: Nationwide Inpatient Sample (1).

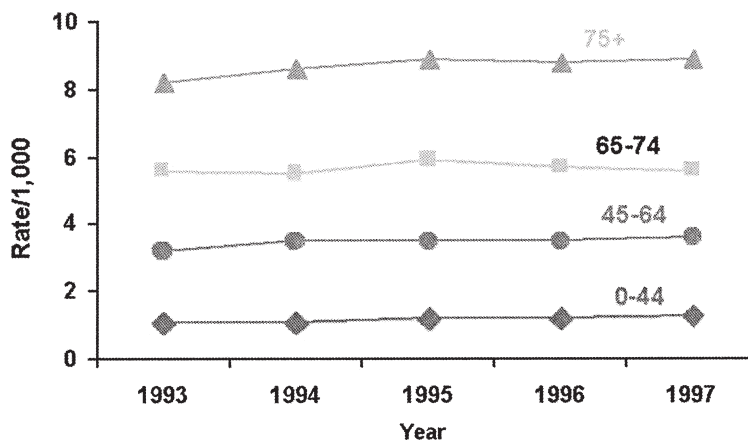


Fig. 6. U.S. hospital discharge rate/1000 for major diabetic nontraumatic lower limb amputations by age, 1993–1997. Source: Nationwide Inpatient Sample (1).

Table 5
Age-Adjusted Population-Based Incident Amputation Rates
in Persons with Diabetes from Select Studies

Study	Population studied	Incidence rate/1000
Humphrey et al. (19), ARG	Nauru	7.6
Humphrey et al. (20) LL	Rochester, MN, USA	3.8
Lehto et al. (21)	East and West Finland	8.0
Morris et al. (22)	Tayside, Scotland	2.5
Moss et al. (40)	Wisconsin, USA	
	Younger onset diabetes	5.1
	Older onset diabetes	7.1
Nelson et al. (23)	Pima Indians, USA	13.7
Siitonen et al. (24)	East Finland	3.4 Men
		2.4 Women
Trautner et al. (25)	Leverkusen, Germany	2.1
Van Houtum et al. (26)	California, USA	4.9
	Netherlands	3.6
Rith-Najarian et al. (13)	Chippewa Indians, USA	
	1986–89	21
	1990–93	12
	1994–96	6

documents that the majority (53%) were performed at the toe, ray, and transmetatarsal level. Figure 6 shows that the discharge rates for lower limb amputation were higher with advancing age.

Age-adjusted rates for lower limb amputations differ by regions of the world. Table 5 shows the variation across populations in age-adjusted incidence rates for nontraumatic lower limb amputations in persons with diabetes. The rates range from 2.1/1000 to 13.7/1000, a sixfold difference (19–26).

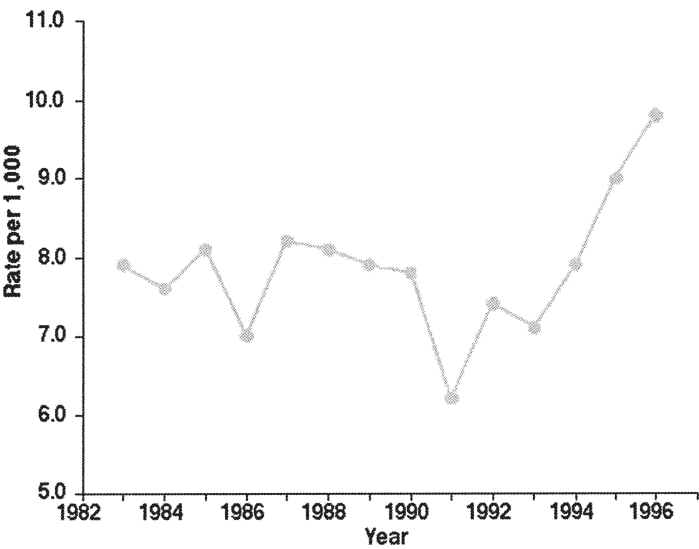


Fig. 7. Age-standardized hospital discharge rate for nontraumatic lower limb amputations in persons with diabetes, U.S., 1983–1996. (Source: National Hospital Discharge Survey, CDC.)

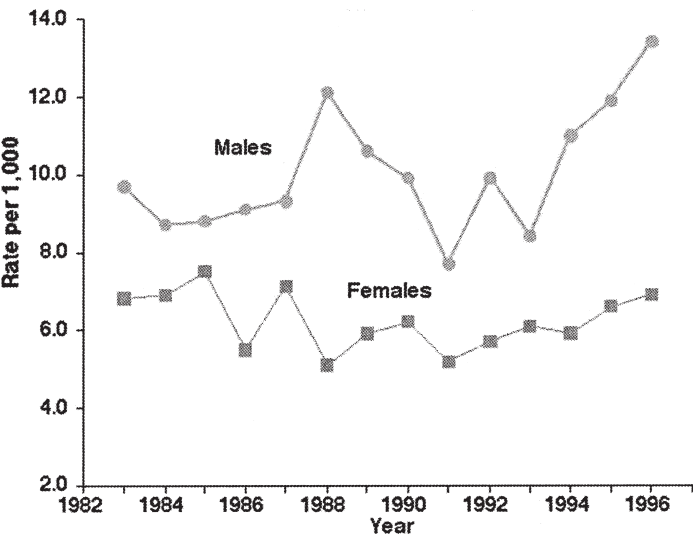


Fig. 8. Age-standardized discharge rate for nontraumatic lower limb amputation in persons with diabetes, by gender, U.S., 1983–1996. (Source: National Hospital Discharge Survey, CDC.)

Trends observed in National Hospital Discharge Survey data for nontraumatic lower limb diabetic amputation in the United States are provocative (2). Figure 7 shows that the U.S. 1996 age-adjusted amputation rate in persons with diabetes was 9.8/1000, an increase of 26% from 1990 (27). Figure 8 presents NHDS findings showing that age-standardized amputation rates were higher in males than females; Figure 9 shows that blacks had consistently higher amputation rates than whites (2).

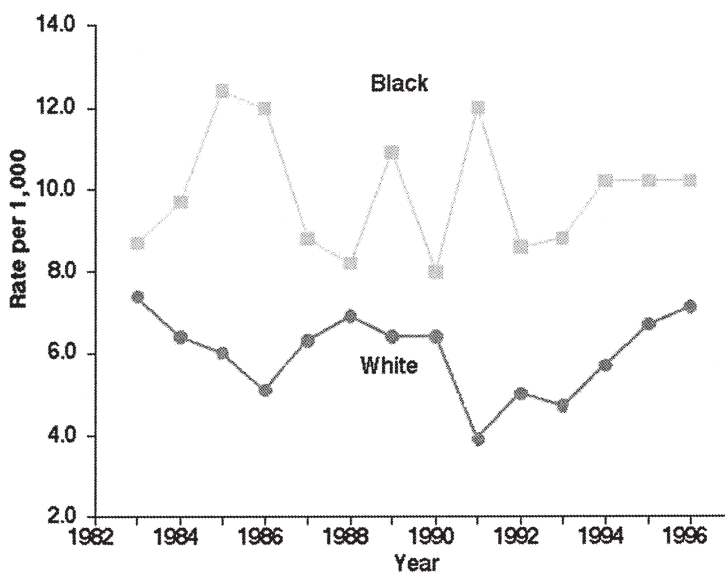


Fig. 9. Age-standardized hospital discharge rate for nontraumatic lower limb amputation in persons with diabetes, by race, U.S., 1983–1996. (Source: National Hospital Discharge Survey, CDC.)

Amputations in black and white Americans with and without diabetes were analyzed in the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Black subjects constituted 15.2% of the cohort and accounted for 27.8% of the amputations. After controlling for the impact of education, hypertension, and smoking, incident and prevalent diabetes were statistically significant predictors of lower limb amputation, but race was not (28).

In the United States there are 306 U.S. hospital referral regions which reflect geographic catchment areas served by major hospitals. Among Medicare recipients with diabetes who underwent a major (transtibial and transfemoral) amputation, there was an 8.6-fold variation in age, sex, and race-adjusted amputation rates, as shown in Figure 10 (28). Only four surgical procedures exhibit higher variation than major amputation in persons with diabetes: lower extremity revascularization, carotid endarterectomy, back surgery, and radical prostatectomy (29). Reasons for the wide variation in procedure rates include discipline-specific training, which may advocate for more or less aggressive limb salvage strategies. Some health care organizations have systems for prophylactic management of diabetic individuals with high-risk foot conditions. Providing this care over time may delay or prevent some foot ulcers and resultant amputations. Another factor is the experience and judgment of the surgeon is in selecting amputation level, surgical technique, and timing of the amputation. These decisions also influence the 10–15% of patients who require a subsequent amputation during the same hospitalization. Patient preferences are also important. Finally, the implication of two-fold higher hospital reimbursement for amputation than limb salvage will be discussed later.

Variation in 1994 hospital discharge amputation rates, for people with diabetes in Wisconsin, shows blacks had 3.1 times, and American Indians had 4.4 times the ampu-

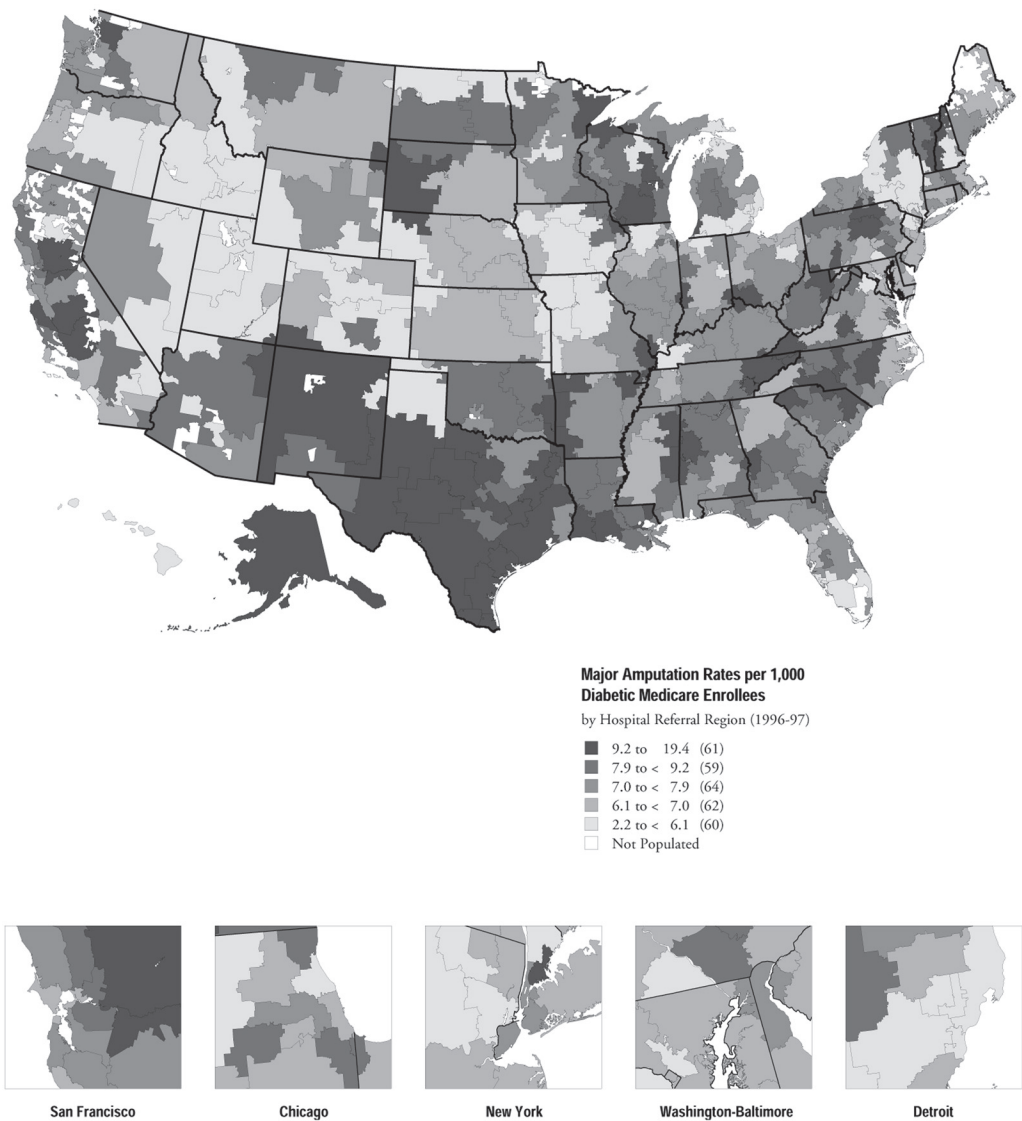


Fig. 10. Major amputation rates/1000 diabetic medicare enrollees by hospital referral region (1996–1997).

tation rates of whites (31). Findings from a 1991 California hospital discharge survey indicated that the age-adjusted amputation rate was 4.4/1000 in Hispanics, 5.6 in non-Hispanic whites, and 9.5/1000 in African Americans (32). In California, amputations in African-Americans were performed at higher levels than in persons from other ethnic and racial groups (33). The importance of education, access to care, and socioeconomic status deserve consideration when assessing racial and ethnic differences and amputations. Both a case-control study performed on patients from a large California health maintenance organization and a prospective case-control study in veterans reported no difference in amputation rates by racial and ethnic status. Patients in these health care systems had access to HMO or VA health care (34,35).

Risk factors for amputation from nine analytic studies that used multivariable analysis are summarized in Table 6. Major independent risk factors are long duration of diabetes, select measures of neuropathy and peripheral vascular disease, high levels of HbA_{1c} or fasting plasma glucose, and a history of ulcers, amputations, and retinopathy (21,23,34–40). The two protective factors identified were provision of outpatient diabetes education (34) and use of aspirin (40). Evidence for these risk factors follows.

Long duration of diabetes was a significant risk factor for amputation in five of the nine studies, and in one it was used as a risk adjuster. Risk for amputation increased with increasing duration of diabetes (21,23,35,38,39).

Diminished or absent peripheral sensation decreases patients awareness of foot pressure, discomfort, and even pain and increases the risk of ulceration and amputation (41). Several measures of peripheral neuropathy were identified as risk factors for amputation. Insensitivity to the 5.07 (10 g) Semmes-Weinstein monofilament was found to increase amputation risk in several studies. However, in the study by Adler et al. (36) this was only significant in the analysis model using TcPO₂. Other measures of peripheral neuropathy associated with amputation risk were absent or diminished bilateral vibration sensation or absent ankle reflexes (21,34).

Measures of peripheral perfusion most commonly employed were AAI, which was associated with lower extremity arterial disease regardless of other symptoms, TcPO₂, and absent or diminished dorsalis pedis and posterior tibialis pulses. TcPO₂ measures cutaneous perfusion and is influenced by the underlying arterial circulation, as well as skin integrity, mechanical effects of repetitive pressure, and tissue edema. Table 6 presents findings from seven studies that directly assessed peripheral vascular function and its relationship to amputation. Adler et al. (36) found that AAI and TcPO₂ were independent predictors of amputation in the final reported models. Absence of peripheral pulses was a risk factor for amputation in three analytic studies (21,36,39); however, in another study absent peripheral pulses were only significant for women in the univariate analysis (38).

Intermittent claudication, absent peripheral pulses, and rest pain are symptoms of lower extremity arterial disease. Palumbo and Melton (9) reported on these variables in the Rochester, MN population. The incidence of lower extremity arterial disease was 8% at diabetes diagnosis, 15% at 10 years, and 45% at 29 years. Intermittent claudication, a fairly benign condition, progressed to rest pain or gangrene in only 1.6% and 1.8% of men and women, respectively, over 10 years (9). In the Framingham Study, intermittent claudication was 3.8 and 6.5 times more common in diabetic than nondiabetic males and females, respectively (42).

Rates of lower extremity arterial reconstruction in the United States were analyzed from 1979 to 1996. Feinglass and colleagues (43) reported that despite large numbers of bypass procedures, balloon angioplasties, endovascular stents, thrombolytic therapies, new imaging techniques, improved antibiotics, and provision of foot care, there was no evidence that major amputation rates had decreased during this decade.

In three analytic studies high blood pressure was an independent predictor of amputation. In two of these studies there was no direct measure of peripheral vascular function (35,40). In the third study, Lee et al. (38) reported that systolic hypertension was significant only in the model for men and diastolic blood pressure was significant only

Table 6
Risk Factors for Lower Limb Amputations in Persons with Diabetes Identified in the Final Analysis Models of Select Studies

Author, type of analysis	Study design, diabetes type	Duration	Neuropathy (monofilament vibration, reflex)	PVD AAI, TcPO ₂ , pulses	HBP	High HbA _{1c} , FPG	Smoking	Ulcer	History Retinopathy	Pt Ed
Adler et al. (36) Multivariate proportional hazards	Cohort, 776 type 1, 2 veterans	0	+	+		0	0	+		
Hamalainen et al. (37) Logistic regression	733 type 1, 2, Finland	Control variable	+	+	0	0	0		+	
Lee et al. (38) Cox regression	Cohort, 875 type 2 Oklahoma Indians	+			+SBP Male +DBP/Female	+ Male	0	0	+	0
Lehto et al. (21) Cox regression	Cohort, 1044 type 2, Finland	+	+	+	0	+	0		+	
Mayfield et al. (39) Logistic regression	Retrospective case-control, 246 type 2 Pima Indians	+	+	+	0	+	0	+	+	
Moss et al. (40) Logistic regression	Cohort, 2990 early- and late-onset, S. WI, USA	0			+DBP	+	+	+	+	
Nelson et al. (23) Stratified	Cohort, 4399 Pima Indians, AZ, USA	+	+		0	+	0		+	
Reiber et al. (34) Logistic regression	Prospective case-control, 316 type 1, 2 veterans	Control variable	+	+	0	+	0		+	+
Selby and Zhang (35) Logistic regression	Nested retrospective case-control, 428 type 1, 2, HMO	+	+		+ SBP	+	0		+	
blank cell, not studied; +, statistically significant finding; 0, no statistically significant finding.										
							AAI, ankle-arm index; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A_{1c}; HBP, high blood pressure; FPG, fasting plasma glucose;			
							Pt Ed, outpatient education; PVD, peripheral vascular disease; SBP, systolic blood pressure; TcPO₂, transcutaneous oxygen tension;			

in the model for women. In this study peripheral vascular function, as measured by peripheral pulses, was not an independent predictor of amputation.

Poor glycemic control has been associated with an increased risk of amputation, primarily through neuropathy pathways. The Diabetes Control and Complications Trial randomized patients with type 1 diabetes to either the intensive blood glucose control group or conventional control. The intensively treated group achieved nearly normal blood glucose levels compared with the control group, whose blood glucose values remained in the conventional range. The intensively treated group had a 69% reduction in subclinical neuropathy, a 57% reduction in clinical neuropathy, and fewer peripheral vascular events than the control group. Elevated HbA_{1c} or plasma glucose was a statistically significant predictor of amputation in seven of the nine analytic studies reported in Table 9 (21,23,34,35,38–40).

The modifiable risk factors for development of atherosclerosis in nondiabetic persons are cigarette smoking, lipoprotein abnormalities, and high blood pressure. These factors are assumed to be similarly atherogenic in diabetic individuals. Smoking was a risk factor in only one study, and only among persons with younger onset diabetes (40). There are several possible explanations for the lack of statistically significant findings in persons with diabetes. Smoking was reported as an infrequent factor by several authors. Other measures of peripheral arterial disease, more proximal in time to the amputation, such as TcPO₂, AAI, or peripheral pulses, may better capture circulation on parameters in the multivariate analyses. An interesting protective association reported by Moss et al. (40) was the significant protective effect of aspirin on lower limb amputation in younger onset patients and a similar, although nonsignificant, trend in older onset patients. Aspirin has long been used as an agent to prevent cardiovascular disease.

Foot ulcer history was an independent predictor of amputation in three studies (36, 39,40). Foot ulcers preceded approx 85% of nontraumatic lower limb amputations in two clinical epidemiology studies (44,45). In studies by Boulton (41) in the United Kingdom and Reiber et al. (46) in the United States, 45–60% of patients with new-onset ulcers reported a prior history of foot ulcer.

Ulcer and amputation risk associated with footwear has been described in several studies. In a study by Edmonds et al. (47), a specialized foot care team achieved high rates of ulcer healing and decreased amputations. Therapeutic footwear was provided to ulcer patients who were then monitored for ulcer recurrences for an average of 26 months. The authors report ulcer recurrences in 26% of persons who wore their special shoes compared with 83% who wore their own footwear. Uccioli et al. (48) randomized patients with a history of prior foot ulcer to therapeutic footwear or their own footwear for a 1-year period. He found a significant decrease in reulceration rates in the group randomized to therapeutic shoes and inserts.

Eight of the nine studies reported retinopathy as an independent predictor of amputation (3,21,23,34,35,37,39,40). Retinopathy may reflect the extent of microvascular disease and may also be a proxy for diabetes severity.

In two studies, patient self-management education and self-care behaviors were linked to a decreased amputation risk. Veterans with high-risk foot conditions were randomized to “usual education” or a 1-hour lecture showing pictures of ulcers and amputations and a one-page instruction sheet. After a 1-year follow-up, persons receiving the special educational session had a threefold decrease in ulceration ($p < 0.005$) and

amputation rates ($p < 0.0025$) (49). A prospective case-control study also in veterans reported a strong protective effect comparing patients who had and had not received prior outpatient education (34). Several foot care intervention programs reported decreases in amputations and reduced days of hospitalizations and costs. The interventions consisted of patient and professional education and changes in organization of foot care services. Given the multidimensional nature of these interventions, many components may have contributed to their success (50–52).

National surveys indicate that only about 50% of patients with diabetes report a foot exam by their health care provider within the past 6 months. Foot exam frequency was lowest in type 2 patients on insulin where only 41% reported foot examinations (12). The frequency of foot exams increased when there were chart reminders or clinician prompts or when the nurse removed the patient's shoes and stockings before the clinician entered the room. Provider foot examination frequency has not been associated with decreased ulcer or amputation rates.

SUBSEQUENT AMPUTATIONS AND MORTALITY

Higher level amputations on the same or the contralateral side are common in diabetic amputees. Table 7 displays the frequency of subsequent amputations by side and as available by year since amputation. Statewide hospital discharge data from California and New Jersey indicated that at 1 year post amputation, 9–13% of amputees experienced a new same-side or contralateral amputation (53,54). Denmark maintains an amputation registry for surveillance purposes (excluding toe amputations). There are 27% of registrants with diabetes and 73% without (55). The Danish Registry reported that 19% of all patients undergoing a major amputation for arteriosclerosis and gangrene had another same-side amputation within 6 months. This percentage increased to only 23% by 48 months following amputation, suggesting that most same-side amputations above the toe level are performed within 6 months of the initial amputation (55).

The study by Braddeley and Fulford (56) reported that 12% of diabetic individuals had a contralateral amputation at 1 year, 23% at 3 years, and 28% at 5 years. According to the descriptive findings available, subsequent contralateral limb amputations occurred in persons with diabetes in 23–30% of amputees at 3 years and in 28–51% at 5 years (56–58). The notable exception was the study from Newcastle-upon-Tyne: the 3-year ipsilateral amputation frequency was 6%, and the contralateral amputation frequency was 3%. This study did report high 3-year mortality rates of 50% (59). Part of the variation in the frequency of ipsilateral and contralateral amputations reported in these studies is related to the age structure and health care of the study population.

Mortality among amputees with diabetes is rarely attributable to amputation and is usually related to concurrent comorbid conditions such as cardiac or renal disease. Table 8 presents amputation mortality data from nine select populations by interval—28 days (perioperative) and 1, 3, and 5 years.

US perioperative mortality from the National Hospital Discharge Survey for 1989 and 1992 was 5.8% (60). Perioperative mortality was 10% in both the Newcastle study and in diabetic amputees in the Department of Veterans Affairs in 1998 (59,61). Reports indicate that the 1-year mortality rates in diabetic amputees range from 13 to 40%, the 3-year mortality rates range from 35 to 65%, and the 5-year mortality rates span 39 to

Table 7
Percent of Individuals with Diabetes and Amputation Undergoing Subsequent Ipsilateral and Contralateral Amputation from Select Studies by Time Interval

Study	Population	1 Year		3 Years		5 Years	
		Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Braddeley et al. (56)	Birmingham, UK Newcastle, UK		12		23		28
Deerochanawong et al. (59)				6	3		
Larsson et al. (44)	Lund, Sweden	14		30		49	
Miller et al. (53)	State of New Jersey, USA	9					
Silbert et al. (58)	New York, USA				30		51
Wright and Kaplan (54)	State of California, USA	13					

Table 8
Percent Mortality in Persons with Diabetes
and Amputation from Select Studies by Time Interval

Study	Population	% Perioperative (28 days)	Years (%)		
			1	3	5
Braddeley and Fulford (56)	Birmingham, UK		16	35	
Deerochanawong et al. (59)	Newcastle, UK	10	40	50	
Ebskov and Josephsen (55)	Denmark; excludes toe amputations ^a		32	55	72
Larsson et al. (44)	Lund, Sweden		15	38	68
Lee et al. (38)	Oklahoma Indians, USA			40	60
Mayfield et al. (61)	US Veterans	10	13	41	65
Nelson et al. (23)	Pima Indians				39
Pohjolainen and Alaranta (62)	S. Finland		38	65	80
Reiber et al. (12)	National Hospital Discharge Survey, USA	5.8			

^a27% of individuals in the Danish Registry have diabetes.

80% (12,23,38,40,44,55,56,59,62). Amputation mortality was also reported to vary by racial and ethnic status. In the 1991 Statewide California Hospital Discharge data, the age-adjusted amputation mortality rates were 1.6% among Hispanics, 2.7% among non-Hispanic whites, and 5.7% among African Americans (32).

ECONOMIC CONSIDERATIONS

Studies on ulcers and amputations usually report only direct patient costs or charges (visits, hospitalizations, procedures, pharmaceuticals, dressings, referrals, and so on), because indirect cost (value of lost income from work, pain, suffering, and family burden, and so forth) is difficult to measure. In assessing the economic impact from ulcers and amputations, the studies by Apelqvist et al. (63) and Ramsey et al. (7) included the entire ulcer episode from lesion onset to final resolution. This methodology captures the many inpatient and outpatient costs/charges associated with foot ulcers and is preferable to reporting only the charges for a single hospitalization or limited time interval.

Table 9 shows the NIS findings for average hospital charges and length of stay in persons with diabetes in 1997. As can be seen, there are conditions in persons with diabetes that account for a higher proportion of hospitalizations and health care charges than do foot ulcers and amputations. Only 3.2% of discharges were for a chronic foot ulcer (ICD 707.1). Figure 11 shows that the average cost for common foot ulcer conditions (chronic ulcers, superficial infections, deep infections, and osteomyelitis) in 1997 was \$16,580. The average length of stay was 8.9 days, 15% longer than in persons with diabetes and no foot ulcer.

Only 1.9% of diabetic discharges was for nontraumatic lower limb amputations. Figure 12 shows the average cost for lower limb amputations in persons with and without diabetes. The average charge for amputation in 1997 by level was toe/transmetatarsal amputation = \$25,241, transtibial amputation = \$31,436, and transfemoral amputation = \$32,214.

Table 9
U.S. Hospital Discharges by Average and Median Charge
and Length of Stay (LOS) for Diabetes and Associated Conditions, 1997

	No.	Total charge (\$)		Average LOS
		Average	Median	
Diabetes, total	4,548,246	14,742	8761	6.3
Foot ulcer (ICD 707.1)	147,110	16,919	10,831	8.9
Lower limb amputation	88,314	26,715	17,302	12.0
Myocardial infarction	256,502	24,500	15,354	6.9
Coronary artery bypass graft	116,759	51,630	42,728	9.9
Stroke	235,914	18,074	11,054	7.7

Data from the Nationwide Inpatient Sample (ref. 1).

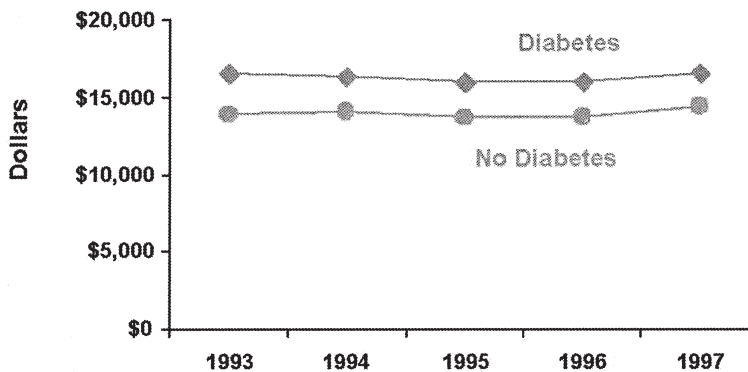


Fig. 11. U.S. total average hospital charges for any ulcer, 1993–1997. Source: Nationwide Inpatient Sample (1).

Foot ulcer costs from three studies are presented in Table 10. The study by Apelqvist et al. (63) followed 314 patients across an entire ulcer episode, from ulcer presentation until final resolution. Healing was achieved in ≤ 2 months in 54% of patients, in 3–4 months in 19% of patients, and in ≥ 5 months in 27% of patients. The 63% of patients who healed without surgery had at an average cost of \$6,664. 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 related to hospitalization was 39% among ulcer patients and 82% among amputees (63).

A nested case-control study was conducted by Ramsey et al. (7) in a large HMO involving 8905 patients with diabetes. In this group, 514 diabetic 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 2 years following the ulcer for both cases and controls. The excess costs attributed to foot ulcers and their sequelae were \$27,987 per patient for the 2-year period following ulcer presentation (7).

Direct cost data on private insurance patients from the MEDSTAT Group, a large U.S. integrated administrative claims system affiliated with private health insurance plans, was analyzed by Holtzer et al. (64). Utilization and cost for the entire ulcer episode may not have been captured from the administrative dataset for all patients in this

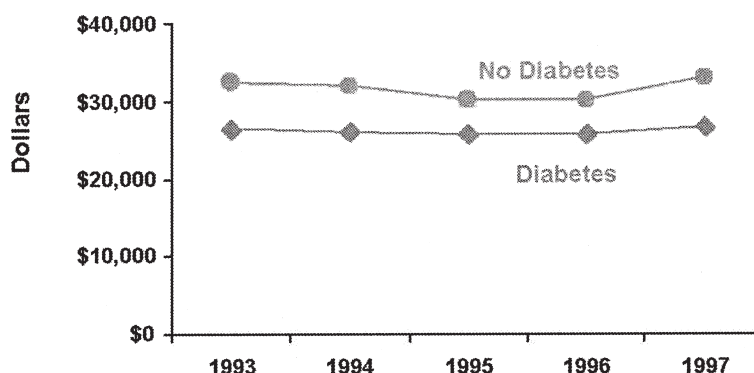


Fig. 12. U.S. total average hospital charges for amputations, 1993–1997. Source: Nationwide Inpatient Sample (1).

Table 10
Direct Cost for Foot Ulcers in Persons with Diabetes from Three Studies

Study	No. of patients, study type	Outcome	Average Episode Cost (US \$)	Inpatient cost (%)	Outpatient cost (%)
Apelqvist et al. (63)	Prospective, 314 general internal medicine patients	Primary healing, 63% Healed after amputation, 24%	\$6,664 \$44,790	61	39
Ramsey et al. (7)	Nested case-control study in HMO of 8905 type 1, 2	Primary healing, 84% Amputation, 16%	\$27,987 total attributable cost	18	82
Holtzer et al. (64)	Retrospective, administrative records of 3013 patients and 3524 episodes	Primary healing, 52% Osteomyelitis, 33% Gangrene/amputation, 14%	\$1929 \$3980 \$15,792	23 23 12	77 77 88

study. Study enrollment criteria were ages 18–64, employed, not on Medicare, and in this system during 1991–1992. Ulcer claims were submitted for 5.1% of diabetic patients. These 3013 patients had 3524 ulcer episodes costing an average of \$4595 per episode. When ulcers were categorized by outcome, the costs were \$1929 for ulcers that healed without complications, \$3980 for those complicated with osteomyelitis, and \$15,792 for patients whose ulcers were complicated with gangrene and required amputation. In this study over 70% of total costs were from hospital settings (64). These direct costs are a conservative estimate for this cross section of persons under age 65, as they exclude amounts paid by the patient and by secondary insurance, episodes of less than 1 week, and individuals who failed to seek treatment.

Reimbursement to hospitals for patients with foot ulcers varies between public and private payers. Table 11 shows that in fiscal year 1998, under DRG reimbursement code 271 (skin ulcer), private insurance companies reimbursed hospitals on average \$11,199

Table 11
Ulcer and Amputation Reimbursement
to Hospitals for Patients with and without Diabetes, 1998

Condition	DRG code no.	MEDSTAT (Private) (66)		Medicare (65)	
		LOS	Average \$ reimbursement	LOS	Average \$ reimbursement
Ulcers					
Osteomyelitis	238	14.1	11,193	8.4	6360
Skin ulcers	271	12.4	10,530	7.2	4567
Cellulitis > age 17 w/cc	277	4.9	5540	5.8	3554
Amputations					
Lower limb amputation, except toe	113	14.1	26,597	11.9	13,413
Toe and upper limb amputation	114	8.0	12,305	8.2	7390
Endocrine amputation	285	9.2	13,253	10.6	110,523

for an average 12.7-day length of stay, whereas Medicare reimbursed hospitals an average of \$4855 (43% of the private reimbursement) for an average 7.9-day length of stay (65,66). Payment for the health care provider is not included in these figures.

In 1998, the average reimbursement to private hospitals for DRG 113, a lower extremity amputation in persons with and without diabetes, was \$26,126 for 14.3 days of hospitalization compared with \$13,512 (51.7%) for an average 13.1 hospital day stay for Medicare patients (65,66). Physician, rehabilitation, outpatient, and other follow-up care costs would be added to these figures for a complete estimate of the direct care costs.

The rise in U.S. amputation rates reported earlier may be influenced by the disparity in reimbursement between limb salvage and amputation in fee-for-service systems. Hospitals are reimbursed almost twice as much for a lower limb amputation as salvage (65,66). Further information on financial impact to health care institutions is provided by the New England Deaconess Hospital. In 100 patients presenting with limb-threatening ischemia between 1984 and 1990, the frequency of diabetic amputation decreased from 44 to 7%, the frequency of popliteal and tibial bypass grafts remained constant, and the frequency of dorsalis pedis bypass grafts increased. The reported length of hospitalization decreased from 1984 levels of 44.1 days for amputees and 34.1 days for bypass graft recipients to 22 days for both groups in 1990. The average bypass graft cost was \$19,808 in 1984 and \$15,981 in 1990; amputation costs were \$20,248 in 1984 and \$18,341 in 1990. Gibbons et al. (67) concluded that even though they were able to improve quality of care, maximize limb salvage, and reduce length of stay and overall cost, their Medicare reimbursement was insufficient and resulted in an average loss of \$7480 per admission (67).

The discharge status of diabetic amputees has been monitored in several populations. In Colorado the percentage of patients discharged to home or self-care gradually declined from 66% for those <age 45 years to 23% for those ages 75 and over. Conversely, as age increased, an increasing proportion required relocation from home or self-care settings to other acute, skilled, and intermediate care facilities for inpatient care (68). In Larsson et al. (44) cohort in Sweden, 93% of patients living independently

before their minor index amputation were able to return to living independently compared with only 61% after a major amputation. Lavery et al. (32) reported that whereas 2.3% of amputees in South Texas were admitted from an institutional care facility, over 25% were discharged to one following amputation (32).

SUMMARY

Persons with diabetes who develop foot ulcers and require lower limb amputations are an important and costly problem in the United States. The hospital amputation discharge rates have increased in the United States in recent years, particularly among males who are members of racial and ethnic minority groups. Many of the independent risk factors for ulcers and amputations identified from population-based, analytic, and experimental studies are similar. Several have the potential for modification by patients and their health care providers. Specific evidence is available demonstrating the benefit of better blood glucose control and self-care strategies learned through patient education. Widespread geographic variation in age, sex, and race-adjusted major amputations suggests that some patients are not receiving optimal care. Further study is needed to address this geographic area variation.

The risk of reulceration is high in persons with a prior foot ulcer. Similarly, once an individual has had an amputation, their risk of a subsequent amputation is approx 10–15% in the first year, approx 23–30% at 3 years, and approx 28–51% at 5 years. Mortality following amputation is about 6% in the first 28 days; thereafter, depending on the study population, mortality increases to an average of 15% at 1 year, 40% at 3 years, and up to 80% at 5 years.

The direct economic cost of foot ulcers and amputation is high and most of these costs are related to hospitalization. The NIS indicated that the average costs for ulcer and amputation, respectively, were \$16,919 and \$26,715. Hospital reimbursement for amputation was nearly double for patients covered by private insurance compared to those covered by Medicare. Hospital reimbursement for care of ulcers is less than half the reimbursement for a lower limb amputation. Patient benefit, quality of life, and rehabilitation potential must be carefully assessed before considering economic trade-offs in decisions regarding limb salvage and amputation.

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