Causal Pathways for Incident Lower-Extremity Ulcers in Patients With Diabetes From Two Settings

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OBJECTIVE— To determine the frequency and constellations of anatomic, pathophysiologic, and environmental factors involved in the development of incident diabetic foot ulcers in patients with diabetes and no history of foot ulcers from Manchester, U.K., and Seattle, Washington, research settings.

RESEARCH DESIGN AND METHODS— The Rothman model of causation was applied to the diabetic foot ulcer condition. The presence of structural deformities, peripheral neuropathy, ischemia, infection, edema, and callus formation was determined for diabetic individuals with incident foot ulcers in Manchester and Seattle. Demographic, health, diabetes, and ulcer data were ascertained for each patient. A multidisciplinary group of foot specialists blinded to patient identity independently reviewed detailed abstracts to determine component and sufficient causes present and contributing to the development of each patient's foot ulcer. A modified Delphi process assisted the group in reaching consensus on component causes for each patient. Estimates of the proportion of ulcers that could be ascribed to each component cause were computed.

RESULTS— From among 92 study patients from Manchester and 56 from Seattle, 32 unique causal pathways were identified. A critical triad (neuropathy, minor foot trauma, foot deformity) was present in >63% of patient's causal pathways to foot ulcers. The components edema and ischemia contributed to the development of 37 and 35% of foot ulcers, respectively. Callus formation was associated with ulcer development in 30% of the pathways. Two unitary causes of ulcer were identified, with trauma and edema accounting for 6 and <1% of ulcers, respectively. The majority of the lesions were on the plantar toes, forefoot, and midfoot.

CONCLUSIONS— The most frequent component causes for lower-extremity ulcers were trauma, neuropathy, and deformity, which were present in a majority of patients. Clinicians are encouraged to use proven strategies to prevent and decrease the impact of modifiable conditions leading to foot ulcers in patients with diabetes.

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Abbreviations: $TcPO_2$, transcutaneous oxygen tension.

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

There are ~16 million diagnosed and undiagnosed diabetic individuals in the U.S. and 1.2 million in the U.K. (1,2). About 15% of them will develop a foot ulcer during their lifetimes (3). Foot ulcers involve a break in the skin's protective covering that extends into or through the dermis and may involve the underlying structural tissues (4). In studies of causal pathways leading to lower-extremity diabetic amputation, foot ulcers preceded ~84% of the amputations (5,6).

Foot ulcers are an important problem in that they *1*) are reasonably common, *2*) are costly, *3*) can identify individuals at high risk for amputation, *4*) affect patients' functional status and well-being, and *5*) may in part be preventable in a majority of patients with medical, self-care, and footwear strategies (7,8). Despite increasing clinical awareness, annual foot ulcer incidence among patients with diabetics is 2–3%, and documented U.S. and U.K. prevalence ranges from 4 to 10% (4).

Foot ulcers are thought to result from a combination of contributing causes. Understanding and quantifying those causes could assist clinicians in targeting practical interventions to reduce the incidence of ulceration. The purpose of this study was to identify and quantity the causal pathways representing the multiple component and sufficient causes involved in development of incident foot ulcers at Manchester, U.K., and Seattle, Washington, sites and to suggest effective strategies for prevention or delay of the most common component causes of foot ulceration.

RESEARCH DESIGN AND METHODS

— Eligible study patients were ages 30–85 years with a diagnosis of diabetes based on laboratory and clinical findings. The patients received care for their first foot ulcer between 1990 and 1994. Patients were enrolled from the Foot Hospital and Clinic, University of Manchester, Manchester, U.K., and the General Internal Medicine Clinic, VA Puget Sound Health Care System, Seattle, Washington. Data routinely collected at the Manchester site included standardized foot and health

Table 1—*Pathophysiology, trauma, and causal pathway definitions*

Callus	Hyperkeratotic formation due to shear stresses, usually in proximity to a bony prominence
Structural foot deformity	Presence of hammertoes, claw toes, hallux valgus, or prominent metatarsal heads
Edema	Swelling of the involved foot or lower-extremity sufficient to leave a clear imprint of the pressure by a finger
Impaired cutaneous circulation	Foot $TcPO_2 \leq 20$ mmHg
Infection	Evidence from physical examination, microbiological culture results, radiology, or pathology reports; includes osteomyelitis
Peripheral ischemia	Impaired arterial circulation of the leg based on absence of palpable lower-extremity pulses or ankle-arm index ≤ 0.70
Minor trauma	An event of either *1*) low pressure and continuing stress or *2*) high pressure and short duration, resulting in a break in the cutaneous barrier or tissue damage
Peripheral neuropathy	Evidence of sensory neuropathy of lower extremities based on *1*) vibratory perception threshold ≥ 25 or *2*) an inability to sense the 5.07 monofilament at any location on the involved foot
Ulcer	A cutaneous erosion characterized by a loss of epithelium that extends to or through the dermis to deeper tissue and is classified as an ulcer by the health care provider
Causal pathway	The minimal set of conditions and events that inevitably produced foot ulcer with none of the conditions being superfluous
Component cause	Causes of interest that were not sufficient in themselves but were required components in one or more distinctive causal chains
Sufficient cause	The onset of disease through the accumulation of multiple component causes or one sufficient cause

Causal pathway terminology adapted from Rothman (10).

examination information on consecutive patients treated for outpatient foot ulcers. The information was obtained for this study both prospectively and retrospectively by a study physician (L.V.). In Seattle, study patients had participated in a longitudinal study of risk factors for diabetic foot ulcers. Extensive foot and health data were prospectively obtained by trained study staff according to research protocols. Excluded from the study at both sites were patients with prior foot ulcers, ulcers above the level of the malleoli, a Charcot foot, and a prior history of lower-extremity amputation. All patients meeting the study criteria at both sites were included.

Data on important, potentially responsible anatomic, pathophysiologic, and environmental factors reported by clinicians and documented in the literature to contribute to foot ulceration were collected as listed in Table 1. Structural foot deformity was the anatomic variable of interest. Pathophysiologic variables included peripheral neuropathy, peripheral ischemia, infection, edema, and callus formation. The environmental variable of interest was minor trauma that resulted in a break in the cutaneous barrier. At the Seattle site, data on trauma preceding lower-extremity ulcer was provided by clinicians; at the Manchester site, data was available from both clinicians and patient self-reports. Additional information was abstracted from clinical and research records on health history, diabetes history, glycemic control, diabetes complications and education, foot care practices, and wound classification. Only the Seattle site provided transcutaneous oxygen tension ($TcPO_2$) findings, which were reviewed for component cause implications among those patients.

The model of causation described by Rothman was used as the conceptual framework for this research (9,10). Causal pathway terminology is defined in Table 1 and illustrated in Fig. 1. A causal pathway is the set of minimal causes (conditions and events) that inevitably produce the outcome ulcer. Figure 1 illustrates the sufficient cause concept wherein one unitary or sufficient cause results in the outcome of interest.

Data on each study patient were compiled into a blinded standardized abstract containing anatomic, pathophysiologic, and environmental factors, ulcer site, clinical and laboratory values, and demographic and health history findings. Five reviewers representing different research and health care specialties (A.J.M.B., E.J.B., L.A.L., D.G.S., G.E.R.) independently reviewed the abstracts and determined the component causes present and contributing to the

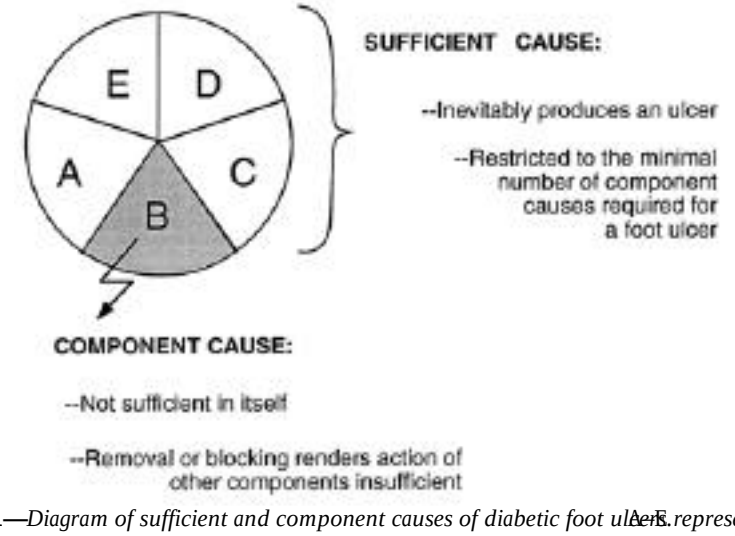

Figure 1—*Diagram of sufficient and component causes of diabetic foot ulcer. A–E represent causes that are not sufficient in themselves but that are required components of a sufficient cause that will inevitably produce the effect. Adapted from Rothman (10).*

Table 2—*Characteristics of patients with lower-extremity ulcers*

	Manchester	Seattle	*P* value
n	91	56	—
Demographic and health care factors			
Age (years)	64.8	64.7	NS
Diabetes duration (years)	14.8	11.6	NS
Male (%)	67.4	100.0	<0.001
White (%)	90.1	83.3	NS
Average HbA_{1c} (%)	15.8	12.2	NS
Ever smoked (%)	53.8	85.2	<0.001
Ankle-arm index (%)			
>0.70	58.7	68.2	NS
0.45–0.7	25.0	17.8	NS
<0.45	10.0	9.3	NS
Foot ulcer location (%)			
Dorsal toes	18.7	25.9	NS
Plantar toes, forefoot, and midfoot	60.4	51.9	NS
Heel	14.3	9.3	NS
Dorsal foot	5.5	11.1	NS
Multiple areas of the foot	1.1	1.9	NS

development of each foot ulcer. The results were tabulated and distributed to all reviewers. A modified Delphi process was used by the reviewers to reach consensus on the causal chains for patients when there was not initial unanimous agreement (11). Consensus was achieved on all patients.

Patient demographic, diabetes, and ulcer characteristics were computed by site and then combined. Comparison of continuous variables used *t* tests, and ordinal variables, χ^2 tests. Unique causal pathways were identified using SPSS software (12). The frequency of each component cause, sufficient cause, and completed causal pathway was computed before and after the modified Delphi process. Unique combinations of component causes in completed pathways were plotted in a frequency matrix. We performed a cluster analysis in SPSS to assess the Euclidean distances between variables (12). Given the methodological limitations of cluster analysis, including the investigative options of setting both the number of clusters and the distance parameters, we describe only the frequency analysis, which parallels the analysis strategy used in the evaluation of causal pathways to limb amputation (5).

RESULTS

The study population included 92 patients from Manchester and 56 patients from Seattle. There were no statistically significant differences by study site in patient age, race, diabetes duration, or HbA_{1c} values, although HbA_{1c} values at both sites were markedly elevated. The upper limits for normal referent values at Manchester and Seattle were 8.5 and 7.0 respectively. As shown in Table 2, Seattle patients were exclusively male. A smoking history was reported by 85% of Seattle patients compared with 54% in Manchester. There were no statistically significant differences between sites in the ankle-arm index values on the affected limb.

The anatomic location of ulcers was similar at both study centers. The plantar surface of the toes and the plantar forefoot and midfoot were the most prominent ulcer sites, followed by the dorsal surface of the toes and the heel. Those ulcer sites combined accounted for 93 and 87% of ulcers in Manchester and Seattle patients, respectively.

The component causes yielded a total of 24 unique pathways among Manchester patients and 32 unique pathways among Seattle patients in both the descriptive and cluster analyses. Table 3 shows the frequency of each component cause in all the completed causal pathways. After grouping data from the two sites, neuropathy was the most common component cause leading to ulceration (78%), followed by a minor traumatic event (77%) and foot deformity (63%). Figure 2 displays this triad of common component causes. Edema, ischemia, and callus formation were present in 37, 35, and 30% of the total ulcer pathways, respectively. For patients from the Seattle site, cutaneous circulation ($TcPO_2$) values were also available, but low levels of $TcPO_2$ appeared as a component cause in only three patients (5.6% of Seattle pathways). Of the two unitary causes of ulcer identified, trauma alone gave rise to ulcers in nine patients (6%), and edema was the sufficient cause in one (<1%).

CONCLUSIONS

Pecoraro and colleagues reported in 1990 that many amputations in diabetic patients were potentially preventable, and that minor trauma, neuropathy, ischemia, and infection were major contributory factors in the causal chain that ultimately resulted in amputation (5). Because 84% of amputations in that series were preceded by foot ulceration, we elected to apply the Rothman model of causation to the etiopathogenesis of foot ulceration in diabetes. There is a need to

Table 3—*Frequency of component causes of foot ulceration by study site*

Component cause	Manchester (*n* = 92)	Seattle (*n* = 56)	Combined (n=146)
Peripheral neuropathy	74	85	78
Callus	28	33	30
Deformity	53	80	63
Impaired cutaneous circulation*	—	5.6	—
Peripheral ischemia	39	30	35
Infection	1.0	2.0	1.0
Edema	29	44	37
Minor trauma	100	39	77
Sufficient cause			
Minor trauma	9.9	—	—
Edema	—	1.8	—

Data are %. *$TcPO_2$ was ascertained only in Seattle.

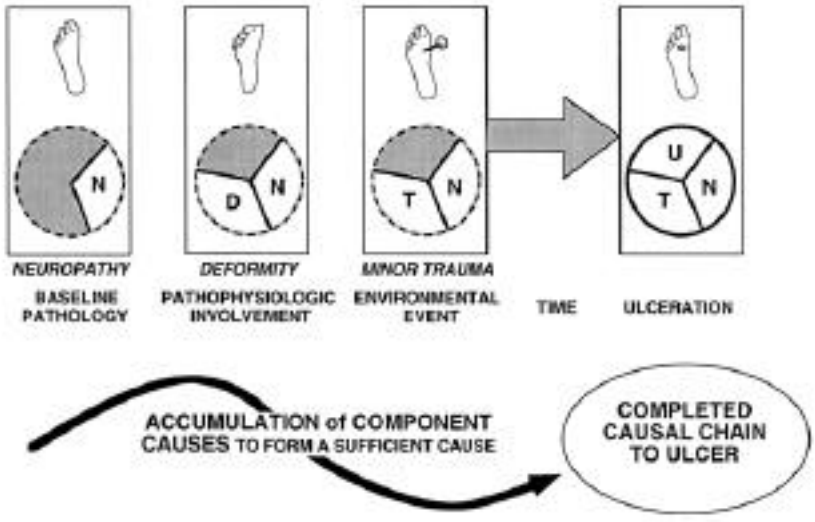

Figure 2—*The most common causal pathway to incident diabetic foot ulcer.*

identify relevant factors given the high prevalence of foot ulcers, the majority of which should be preventable (8). Thus, defining causal pathways to ulceration should suggest practical interventions that could reduce the incidence of ulceration and amputation.

Patients with incident foot ulcers were selected for this research to minimize the possibility that the causal pathways observed would be influenced by existing scar tissue or by abnormal dermal, subcutaneous, and underlying tissue, which has been reported to be more fragile and vulnerable to shear forces of walking than tissue not previously ulcerated (13).

We identified three components that were present in the majority of pathways leading to incident foot ulcers: peripheral neuropathy, minor trauma, and foot deformity. Peripheral neuropathy was the most common component cause and was present in 78% of the ulcer pathways. This common, long-term complication of diabetes has an estimated prevalence ranging from 28.5% to nearly 50% (14–16). In a prospective study, Young et al. (17) demonstrated that the presence of peripheral neuropathy increased the risk for foot ulceration nearly sevenfold. Similarly, in a case-control study by McNeely et al. (18), the adjusted odds ratio for an absent ankle reflex was 6.5 (95% CI 2.4–18.1) and the odds ratio was 18.4 (95% CI 3.8–88.5) for insensitivity to the 5.07 monofilament (18), a semiquantitative measure used to assess the threshold for light touch-pressure.

Structural foot deformities were common in patients at both study sites, although additional research focus on foot deformities at the Seattle site could have contributed to a higher recognition rate for the condition. Neuropathic changes in people with diabetes result in decreased sensation and proprioception and weakened intrinsic muscles of the foot, which may lead to the toes being pulled up into a hammer toe or clawfoot flexion deformity. Such a deformity would increase the pressure on the tops of the toes and under the metatarsal heads. Additionally, there may be distal migration of the plantar fat pad covering the metatarsal heads and a flattened transverse or longitudinal arch. Thus, patients with foot deformities develop bony prominences, especially under the metatarsal heads (19). In persons lacking protective sensation, there may be an increased risk of pedal ulceration due to unperceived repetitive pressure and shear stress. Masson et al. (20) found that, despite similar frequencies of bony deformities in the feet of patients with diabetes (n = 38) and rheumatoid arthritis (n = 37), 32% of diabetic individuals had a prior history of foot ulcer compared with none of those with arthritis. Veves et al. (21) showed that nearly half of neuropathic patents with high plantar pressures ulcerated over a 2.5-year follow-up period.

Minor trauma was an important component and sufficient cause of ulceration. Many patients with advanced sensorimotor neuropathy lack mechanisms to identify lower limb pain, pressure, or trauma (for instance, a nail protruding into the shoe or shoes that are too tight). Our finding, that 77% of all ulcer pathways included trauma, was similar to the report that 81% of causal pathways for diabetic limb amputation included trauma (5).

Peripheral edema was a component in 37% of ulcer pathways and frequently occurred in conjunction with minor trauma, often footwear-related. Edema often accentuates the mismatch between a patient's foot shape and shoe. Cutaneous circulation,

Table 4—*Promising strategies to prevent or delay development of common component causes of foot ulceration*

Component cause	Prevention strategy
Peripheral neuropathy	Patient instruction on how the lack of protective sensation requires special patient/family and provider care
	Referral to outpatient education
	Protective footwear
	Good glycemic control
Deformity	Appropriate shoes and inserts to accommodate contours of the foot and relieve pressure
	Education to support footwear
Minor trauma	Protective footwear
	Review residential environment for safety
	Patient education
Peripheral ischemia	Alter risk factors for atherosclerosis (hypertension, smoking, lipoprotein abnormalities)
	Revascularize for critical ischemia
Callus	Regular removal of callus
	Footwear that minimizes callus development
Peripheral edema	Footwear accommodative to presence/absence of edema
	Resolution of edema based on etiology (pharmacologic approaches, compression stockings, bedrest)

measured as $TcPO_2$, reflects the integration of capillary oxygen, metabolic demand, and nutrient delivery that occurs at the level of the skin. Pecoraro (22) reported low peripheral cutaneous circulation in diabetic individuals presenting with extensive edema; the circulation improved markedly after treatment and resolution of edema. In our study, $TcPO_2$ values were only available for Seattle patients and were a component cause in only three individuals.

Lower-limb ischemia was a component cause in 35% of study pathways but was not a sufficient cause of foot ulcer for any patient. McNeely reported no increased risk for ulceration associated with an abnormal ankle-arm index (18). In the reported research on pathways to lower-extremity amputation, peripheral ischemia was a component cause in 46% and a sufficient cause in 5% of pathways (5).

Callus or hyperkeratosis was a component cause in 30% of pathways. Areas where the foot is exposed to increased pressure over time may develop callus, which acts like a foreign body and further increases pressure leading to tissue breakdown and ulcer formation under the callus. One prospective study demonstrated that plantar calluses were a strong predictors for foot ulcers and that ulcers recurred only at the sites of callus (23). In another study, athletic running shoes decreased plantar callus formation, reduced the need for debridement by threefold, and reduced the complaints of painful callus from 70 to 9% (24).

The very low frequency of infection in these outpatients was not surprising in that infection would be unlikely as part of the causal chain leading to foot ulcers; rather it would become operative after ulcer development. The 1% overall frequency of infection as a component cause for foot ulcer is contrasted with a 59% frequency in the reported study of pathways to lower-limb amputation (5).

The majority of the study ulcers were located on the plantar surface of the toes, forefoot, and midfoot. The dorsal toe location, however, accounted for 19 and 26% of ulcers in Manchester and Seattle, respectively.

Clinical implications

Table 4 reviews strategies to prevent or delay the component causes of foot ulceration. The most common component cause was neuropathy. Detection of clinically significant sensorimotor deficits is simple and inexpensive and can be performed by the primary care physician with a Semmes-Weinstein monofilament. Inability to sense the monofilament has been associated with an increased risk of foot ulcer (25). The loss of protective sensation in the foot is insidious; thus this simple test for protective sensation may be very informative to patients and providers. Loss of protective sensation is an indication that closer clinical follow-up, intensive education, and consideration of special footwear are all indicated (26). Good glycemic control for patients with diabetes is also recommended as a means to prevent or delay the development of peripheral neuropathy (27).

Shoe-related minor trauma has been reported as a frequent event leading to ulcers and amputations (28,29), and protecting the insensate foot with appropriate footwear has been shown to be effective in ulcer prevention (30). Proper footwear selection can relieve areas of excessive plantar pressure; reduce the formation of callus; reduce shock and shear stress; accommodate, stabilize, and support deformities; and protect the foot from external trauma that can lead to ulceration (31). The frequency of ulcers on the plantar and dorsal surface of the toes in this study suggests opportunities for footwear modifications. Shoes of a forgiving material, preferably leather, should be used to accommodate wider and mildly deformed feet.

Lower-limb edema, depending on etiology, may be reversed with aggressive medical treatment of cardiac conditions, bedrest and leg elevation, compression stockings, and antibiotic treatment of cellulitis. Accommodative footwear can diminish the likelihood of minor shoe-related trauma. There is evidence that revascularization procedures may be effective for selected patients with vascular insufficiency (32). Surgical correction of the bony deformities of the foot, including resection of the metatarsal head, has been reported to decrease the plantar pressure and improve ulcer healing but has not been rigorously evaluated against other management strategies. Removal of callus under the forefoot using a scalpel or abrasive device can reduce the peak plantar pressures by 29% (33). The rate of callus formation can also be decreased by footwear that cushions the sole (24).

In summary, potentially preventable components have been identified that appear in the causal pathways leading to foot ulcers. The clinical and public health response should target removal of one or more component causes to prevent or delay the development of a foot ulcer. Available evidenced-based research findings support a more systematic approach by clinicians and patients to preventing the occurrence of foot ulcers in patients with diabetes.

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