Diabetic Neuropathic Foot Ulcers

The association of wound size, wound duration, and wound grade on healing

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OBJECTIVE — The goal of this study was to evaluate whether simple risk factors can be identified that successfully characterize who will heal and who will not heal among patients who have received standard therapy for diabetic neuropathic foot ulcers.

RESEARCH DESIGN AND METHODS — For this cohort study, we evaluated >31,000 individuals with a diabetic neuropathic foot ulcer seen in the Curative Health Services System. Using multivariate logistic regression, we evaluated the association between wound size, wound duration, wound grade, and other variables and their effect on whether a patient would heal by the 20th week of care.

RESULTS — We demonstrated that wound size, wound duration, and wound grade are all significantly associated with the likelihood of a wound healing by the 20th week of care. In addition, we noted that these associations were not significantly affected by the treating wound care center, whether the unit of analysis was one wound on a patient or all of their wounds, or current adjuvant therapies.

CONCLUSIONS — We have shown that three easy-to-measure risk factors are associated with a wound healing. These results should help clinicians understand the likelihood that a wound will heal and help those conducting clinical investigations to design better trials.

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Lower-extremity ulcers are a serious complication of diabetes. More than 16 million people in the U.S. have diabetes, and 15% of them can expect to develop a foot ulcer at some point in their lives (1–3). Diabetic patients admitted to the hospital with lower-extremity ulcers were hospitalized longer on average than those who were hospitalized and did not have ulcers (1,3). Whereas only 4% of the population has diabetes, 46% of those admitted to a hospital with a foot ulcer had diabetes, and half of all lower-extremity amputations in hospitalized patients occurred in diabetic patients (1,3). Those with a lower-extremity amputation have a diminished quality of life and increased health costs, often have many concomitant medical ailments, are more likely to have the contralateral limb amputated, and are more likely to die within the next 5 years than those with no amputation (4,5).

There are many pathways for the development of a diabetic foot ulcer. In general, they include a combination of lower-limb arterial insufficiency, lower-limb diabetic neuropathy, and local trauma (6). About 20% of diabetic patients with foot ulcers will primarily have inadequate arterial blood flow, ~50% will primarily have diabetic neuropathy, and ~30% will be afflicted with both conditions (1,6). Inadequate arterial blood flow is usually treated by a variety of surgical techniques that improve blood flow (7). For this study, foot ulcers on individuals with diabetes who lack protective sensation and have adequate arterial blood flow to their foot are termed diabetic neuropathic foot ulcers (DNFUs) (8–10).

The treatment of a DNFU usually consists of debridement of necrotic tissue, use of a moist wound dressing, and the use of a device that protects the wound from pressure or trauma related to ambulation and other acts of daily living. Several devices are commonly used, including contact casts, crutches, wheelchairs, and special footwear (9,11–15). This type of care is often the standard care arm in randomized clinical trials and was recently discussed in a consensus statement from the American Diabetes Association (8–12,15).

Recently the U.S. Food and Drug Administration approved several new treatments, making this an exciting time for those who treat patients with DNFUs (8–10,12,16). These agents represent two new treatment classes, growth factors and cell therapies, and are used in combination with the standard therapy described above. Even with the advent of these new products, success in treating DNFUs is dismal. About 10–33% of the patients in the standard-care arms of clinical trials will heal by 12–20 weeks of care, whereas ~30–50% of the individuals that receive one of the new products will heal by 12–20 weeks of care (8–10,12,16).

We hypothesize that several risk factors can be identified that are associated with a DNFU healing by the 20th week of standard care. This information is important to clinicians—it should help them decide who might respond to standard therapy, who might be better off receiving an adjuvant early in the treatment plan, and who should receive specialized care. The goal of this study was to evaluate

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Abbreviations: CHS, Curative Health Services; DNFU, diabetic neuropathic foot ulcer; GEE, generalized estimation equation; GLLAMM, generalized linear latent and mixed model; OR, odds ratio.

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

Table 1—*The CHS wound grade scale*

Wound grade	Stage description
1	Partial thickness involving only dermis and epidermis
2	Full thickness and subcutaneous tissues
3	Grade 2 plus exposed tendons, ligament, and/or joint
4	Grade 3 plus abscess and/or osteomyelitis
5	Grade 3 plus necrotic tissue in wound
6	Grade 3 plus gangrene in the wound and surrounding tissue

whether risk factors can be identified to successfully characterize those patients with a DNFU who will heal and who will not heal.

RESEARCH DESIGN AND METHODS

Patient population

Since 1988, Curative Health Services (CHS) has managed >150 distinct wound care facilities in 38 states in the U.S. and has maintained an administrative and patient record database (17). We have previously demonstrated via chart review the validity of using this database to study individuals with DNFUs (17,18). Briefly, in that study, we showed that we could use the database to accurately determine whether a subject had a diagnosis of DNFU and healed by the 20th week of care compared with the medical record (positive predictive values of 98% [95% CI 0.89–0.99] and 93% [0.68–0.99], respectively) (18). In the medical record, arterial flow abnormalities were determined noninvasively by $TcPo_2$ monitoring or arterial Doppler and neuropathy by the absence of a response to a 10-g Semmes-Weinstein filament. By using this algorithm, we specifically did not study individuals with significant lower-limb arterial disease.

Subjects for this investigation had been treated at a CHS center between 1988 and 2000 and had at least one DNFU. We analyzed the subject's only or most recent registration period. To clarify, for a subject who was successfully treated, stopped receiving care at a CHS center, and then returned for care (i.e., re-registered), only the last cycle of wound care was analyzed. Furthermore, to avoid including subjects who were one-time specialty center consultations, any individual who did not have a second office visit or documentation of a surgical procedure within 6 weeks of the first office visit was excluded.

Outcome and risk factors

For all subjects, the outcome—a healed wound by the 20th week of care—was determined using a previously validated algorithm (18). We selected this outcome because this is the longest end point consistently used in clinical trials. We also evaluated a 12-week end point. The results from this analysis were similar to those reported below.

For this study, a risk factor was a subject or wound characteristic noted at the first office visit that might play a role in causing or explaining the outcome. The following risk factor variables were evaluated: patient age, patient sex, duration of the wound (months), size of the wound (mm^2), wound grade (Table 1), number of wounds, prior care at a CHS center, and which CHS center. Prior care was defined by determining if the patient had previously received a full cycle of care (i.e., they previously had been registered by, treated by, and discharged from active care at a wound care center).

Analysis

All risk factor variables were characterized by estimating means, SDs, medians, and quartiles and by a visual assessment with a particular focus on skewing. Two variables in this data set, duration of the wound and wound size, were severely skewed (see RESULTS). These variables were log transformed to a more symmetric distribution. For the initial analyses, we used univariate assessments of association, such as 2×2 tables, χ^2 statistics, Mantel-Haenszel statistics, and one-way ANOVA.

Our primary question was to estimate the association of various risk factors with the probability that a patient with a DNFU would heal by the 20th week of care. To assess the magnitude of the effect of a given risk factor, we used single-variable (unadjusted) and multiple-variable (fully adjusted) logistic regression models to estimate odds ratios (ORs). Both unadjusted and fully adjusted ORs are reported with 95% CIs. Fully adjusted ORs were calculated by including all risk factor variables. Two-way interaction terms were evaluated. Both fixed effects and random effects models using generalized estimating equations were calculated (19). Finally, to simultaneously evaluate the effects of clustering due to wound care center and patient, we evaluated effect estimates using a generalized linear latent and mixed model (GLLAMM) (20). These techniques adjust the variance estimates because multiple observations may have been made within nonindependent units, such as a subject or wound care center. All analyses were conducted using SAS version 8 or STATA 7, or both, for a PC.

RESULTS — The 31,106 individuals who met our criteria for a DNFU had a total of 72,525 wounds (Table 2). Of the patients, 53.9% were men, and 20.5% had previously received care at a wound care center. The mean patient age was 63.8 years. Of the wounds, 76.2% were grade 2 or lower. Before log transformation, the mean duration of a wound was 5.39 months and the median duration of a wound was 1.0 months. The mean on the log scale was 0.48 log months (geometric mean 1.6 months), SD 1.39. Before log transformation, the mean size of a wound at presentation was 588.6 mm^2 and the median size of a wound was 118.0 mm^2. The mean on the log scale was 4.86 log mm^2 (geometric mean 196 mm^2), SD 1.68. By the 20th week of care, 50.3% of the wounds healed. The percentages of wounds not healed for each risk factor are listed in Table 2.

Men were slightly less likely to heal (Table 3). Wounds on individuals with increasing numbers of wounds, wounds that were larger (log mm^2), and wounds that were older (log months) were all less likely to heal. Wounds of increasing grade were also less likely to heal. We dichotomized wound grade, as presented in Table 1, as a grade of ≤2 vs. >2. This dichotomization is consistent with most randomized clinical trials in that they generally included only patients of grade 2 or lower (8,10,12,21). Unexpectedly, those who had previous wounds were more likely to heal. With the exception of wound grade, the unadjusted versus fully adjusted effect estimates did not differ by >10%, indicating that the unadjusted estimates were not confounded by the other risk factor variables (22). Several two-way interac-

Table 2—*The prevalence of a wound not healing for a given risk factor* (N = *72,525 wounds*)

Risk factor	Percent not healed
Age <54 years	48.9
Age 55–64 years	48.4
Age 65–74	49.0
Age >74 years	52.5
Male	50.7
Female	48.5
Wound grade 1	36.2
Wound grade 2	44.7
Wound grade 3	60.7
Wound grade 4	67.1
Wound grade 5	78.7
Wound grade 6	91.5
Wound grade 1 or 2	44.1
Wound grade 3, 4, 5, or 6	67.4
Wound log duration ≤0.50 log months	40.9
Wound log duration >0.50 to ≤1.00 log months	46.5
Wound log duration >1.00 to ≤4.00 log months	53.0
Wound log duration >4.00 log months	59.1
Would log area ≤39 log mm^2	35.9
Wound log area >39 to ≤118 log mm^2	44.5
Wound log area >118 to ≤401 log mm^2	52.6
Wound log area >401 log mm^2	67.0
Total number of wounds 1	46.6
Total number of wounds 2	48.2
Total number of wounds 3	50.4
Total number of wounds 4 or more	51.5
Prior visit	50.6
No prior visit	46.3

Age, wound log duration, wound log area, and patient age categorized by quartile. Data is for all wounds and not by individual or primary wound.

tions were evaluated: wound grade and duration, wound grade and area, wound grade and wound count, and duration and area. Whereas many of these interactions had *P* values of <0.01, the clinical significance of these interactions was less clear because the effect estimates for any specific wound grade varied very little compared with the fully adjusted point estimates (Table 2). For example, the largest change in the effect estimate of wound log duration occurred between wound grades 1 and 5 (OR 1.25 [95% CI 1.14–1.24] and 1.13 [1.05–1.22], respectively), and the largest change for wound log area occurred between grades 1 and 5 (1.19 [1.14–1.24] and 1.34 [1.26–1.42], respectively).

Some patients received an adjuvant treatment in association with standard therapy. Entering adjuvant therapies (platelet releasate, recombinant human platelet-derived growth factor, or graft skin) into our multivariate model did not change the point estimates of any of our risk factor variables by >10% (22). The results also did not differ if these patients were dropped from the analysis.

Because multiple patients may have been treated at the same wound care center and more than one wound per patient may have been used in our investigation, the data in our investigation may lack true independence. To evaluate this effect with respect to wound care center, we first entered each center, as a categorical variable, into a logistic regression model. Patient care by a specific center, compared with any other center, was not associated with wound healing. Next, we added each center as a categorical variable into the multivariate model containing all of our risk factors. This adjustment did not alter any of the fully adjusted effect estimates reported in Table 2 by >10% (22). Finally, we ran generalized estimation equations (GEEs) to compensate for the lack of independence due to wound care center, patient, and wound care center and patient simultaneously. We also ran this model clustering on patient and a GLLAMM model clustering on both patient and hospital. The GEE- and GLLAMM-estimated confidence intervals did not vary substantially from those presented in Table 3. Finally, it should be noted that for most clinical trials only one wound is enrolled and evaluated. To determine whether the effect estimates for our risk factor variables might be different for a single wound than for all of the wounds, we repeated our analyses only including the first or primary wound on an individual cared for in a wound care center. As can be noted in Table 3, the effect estimates for a single wound are not different by >10% from the effect estimates for all wounds.

CONCLUSIONS — Multiple clinically relevant risk factors exist that can be used to distinguish between a wound that is likely to heal and one that is not likely to heal by the 20th week of standard therapy

TABLE 3—*ORs and 95% CIs for risk factors by wound*

Risk factor	Unadjusted	Adjusted	Adjusted single wound*
Sex	1.09 (1.06,1.12)	1.07 (1.03,1.12)	1.14 (1.08,1.20)
Prior wounds	0.84 (0.81,0.87)	0.92 (0.89,0.96)	—
Grade†	2.61 (2.52,2.71)	2.05 (1.98,2.13)	1.93 (1.82,2.05)
Age	1.00 (1.00,1.00)	1.00 (1.00,1.01)	1.01 (1.00,1.01)
Count	1.07 (1.06,1.08)	1.12 (1.11,1.14)	—
Wound duration†‡	1.23 (1.22,1.25)	1.23 (1.21,1.24)	1.30 (1.27,1.32)
Wound size*†‡	1.36 (1.35,1.37)	1.31 (1.29,1.32)	1.32 (1.30,1.34)

All $P < 0.0001$. *Analysis contained only the patient's first or primary wound. These patients could therefore not have a prior wound visit. †$P < 0.0001$. ‡Log-transformed wound duration measured as log months, and wound size measured as log mm^2.

for a patient with a DNFU. The risk factors or wound characteristics that most dramatically are associated with a wound failing to heal are increasing wound size, increasing wound duration, and the grade of the wound. More simply, wound grade can be redefined such that wounds are differentiated by whether they penetrate through the subcutaneous fat layer (i.e., grade 3 or higher). It is these that are less likely to heal. These risk factor variables are clinically relevant enough that they should be evaluated during the first office visit by the physician or health care provider caring for a patient with a DNFU.

The association between two risk factor variables and wound healing may be confusing. These risk factors are prior wounds (patients with prior wounds were more likely to heal) and the use of adjuvant therapies (those that used adjuvants were less likely to heal). We believe that the explanations for these associations are similar and related to selection bias. We hypothesize that those who had prior wounds were more likely to seek care at the wound care center that successfully treated them in the past. In other words, those who successfully responded to the wound care center environment were likely to return and likely to be successful again. With respect to use of a treatment adjuvant, these therapies did not start at the first office visit, so it is unlikely that a patient received a full 20 weeks of care with adjuvants (i.e., our evaluation of these therapies is incomplete). Second, because these therapies often did not commence until week 8 or 12, it is very likely that physicians selected those patients that appeared to be doing poorly for adjuvant care. In fact, in a previous publication in which we evaluated the use of platelet releasate using a statistical technique that models selection bias, we were able to show that the most severe wounds received this adjuvant treatment and that it was effective (17).

Recently, Oyibo et al. (23) evaluated the association of several risk factors, including wound size and measured wound depth (similar to our wound grade), with healing in patients with diabetes and foot ulcers. Their cohort study included 194 patients evaluated in a foot ulcer center in England and a center in Texas. As in our study, they noted that the size of the wound correlated with the time required for a wound to heal. Unlike our study, the tissue depth of the wound (our wound grade) was not predictive of time to healing but did predict amputation risk. Many other risk factors did not correlate with healing, including age and sex of the patient, type of diabetes, duration of diabetes, and ulcer site. Their study differed from ours in that they evaluated only one wound per patient; our patients on average were older, more of our patients were female, all of our patients were neuropathic with good arterial flow, we evaluated healing by the 20th week of care and present the odds of healing, and our study was larger and multicentered.

In fact, one of the greatest strengths of our study is its sheer size and the geographic distribution of wound care centers throughout the U.S. Because our data source was CHS wound care centers, it is possible (but we believe unlikely) that the results of this study do not generalize to independent practitioners or those who do not frequently treat individuals with DNFUs. It is also important to note that wound care center was not a significant confounding variable. In other words, wound duration, wound size, and wound grade had similar effects in all centers. Furthermore, adding wound care center did not significantly improve our models. It seems likely that because CHS requests that local wound care centers follow their protocols—which include discussions about debridement, good wound care, offloading, etc.—it is possible to successfully educationally intervene across a large network of wound care specialists. Finally, it should be noted that the association of wound size and wound duration with wound healing has been noted in meta-analyses of clinical treatment trials for DNFUs and venous leg ulcers, another chronic wound (15,24,25).

There are several limitations to this study that are common to observational database studies. We discussed selection bias above. Information bias may have also affected our results. First, there may have been systematic differences between the reporting of those who did and did not have particular risk factors. Based on the risk factors that we evaluated, this is unlikely—our risk factors were basic to the initial evaluation of a chronic wound. Second, it is possible that there were systematic differences between the way risk factors were measured and the likelihood that a wound would heal. For example, it is possible that during the first patient visit the physician undermeasured wounds that were likely to heal and overmeasured wounds that were unlikely to heal. We believe that this is unlikely because wound size is also used to monitor the progress of a wound. In addition, those recording the data were not aware of our study. Finally, as with all observational studies, the evaluation of risk factors and confounding factors is limited to variables accurately and consistently present in a database. For this study, we were not able to evaluate glycosylated hemoglobin (which was previously shown not to influence wound healing [24]), fasting blood glucose, presence of retinopathy or nephropathy, body weight, location of the ulcer, degree of foot deformity, or the use of or compliance with treatments used for diabetes.

In summary, we have shown that at the initial visit, the size of the wound, the age of the wound, and the grade of the wound are all predictors for the failure of a neuropathic foot ulcer to heal. These are simple risk factors that are easily measured at the initial office visit. In most cases, they are already part of the initial patient assessment. We believe that, taken together, these risk factors argue for the early treatment of individuals with foot ulcers. The association of these risk factors with a wound healing is the same whether the wound receives standard care or standard care plus an adjuvant (such as a topical growth factor). More importantly, we have demonstrated that these associations depend on the wound and that they do not vary from wound care center to wound care center. Finally, our results are important to clinicians caring for patients with DNFUs in that it is possible to characterize those wounds that will do well with medical therapy and those that will not. In addition, for those designing trials, we believe that it is prudent that these risk factors be considered both when choosing whom to accept into a trial and when assessing the effect of a novel therapeutic.

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References

1. National Diabetes Data Group: *Diabetes in America*. Vol. 2. Bethesda, MD, National Institutes of Health, 1995 (NIH publ. no. 95–1468)
2. McNeely MJ, Boyko EJ, Ahroni JH, Stensel VL, Reiber GE, Smith DG, Pecoraro RE: The independent contributions of diabetic neuropathy and vasculopathy in foot ulceration. *Diabetes Care* 18:216–219, 1995
3. Reiber GE: The epidemiology of diabetic foot problems. *Diabetic Medicine* 13:S6–S11, 1998
4. Brod M: Quality of life issues in patients with diabetes and lower extremity ulcers: patients and care givers. *Qual Life Res* 7:365–372, 1998
5. Ashry HR, Lavery LA, Armstrong DG, Lavery DC, van Houtum WH: Cost of diabetes-related amputations in minorities. *J Foot Ankle Surg* 37:186–190, 1998
6. Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA, Boulton AJ: Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes Care* 22:157–162, 1999
7. Tannenbaum GA, Pomposelli FB, Marcaccio EJ, Gibbons GW, Campbell DR, Freeman DV, Miller A, LoGerfo FW: Safety of vein bypass grafting to the dorsal pedal artery in diabetic patients with foot infections. *J Vasc Surg* 15:982–990, 1992
8. Gentzkow GD, Iwasaki SD, Hershon KS, Mengel M, Prendergast JJ, Ricotta JJ, Steed DP, Lipkin S: Use of Dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes Care* 19:350–354, 1996
9. Wieman TJ, Smiell JM, Su Y: Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. *Diabetes Care* 21:822–827, 1998
10. Veves A, Falanga V, Armstrong DG, Sabolinski ML, Apligraf Diabetic Foot Ulcer Study: Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care* 24:290–295, 2001
11. American Diabetes Association: Consensus development conference on diabetic wound care. *Diabetes Care* 22:1354–1360, 1999
12. Steed DL: Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group. *J Vasc Surg* 21:71–78, 1995
13. Weiman TJ, Griffiths GD, Polk HC: Management of diabetic midfoot ulcers. *Ann Surg* 215:627–632, 1992
14. Steed DL: Foundations of good ulcer care. *Am J Surg* 176 (Suppl. 2A):20S–25S, 1998
15. Margolis DJ, Kantor J, Berlin JA: Healing of diabetic neuropathic foot ulcers receiving standard treatment: a meta analysis. *Diabetes Care* 22:692–695, 1999
16. Steed DL, Goslen JB, Holloway GA, Malone JM, Bunt TJ, Webster MW: Randomized prospective double-blinded trial in healing chronic foot ulcers. *Diabetes Care* 15:1598–1604, 1992
17. Margolis DJ, Kantor J, Santanna J, Strom BL, Berlin JA: Effectiveness of platelet releasate for the treatment of diabetic neuropathic foot ulcers. *Diabetes Care* 24:483–488, 2001
18. Kantor J, Margolis DJ: The accuracy of using a wound care specialty clinic database to study diabetic neuropathic foot ulcers. *Wound Repair Regen* 8:169–173, 2000
19. Begaud B, Moride Y, Tubert-Bitter P, Chaslerie A, Haramburu F: False-positives in spontaneous reporting: should we worry about them?. *Br J Clin Pharmacol* 38:401–404, 1994
20. Rabe-Hesketh S, Pickles A, Skrondal A: *GLLAMM Manual*. London, Institute of Psychiatry, King's College, University of London, 2001
21. Steed DL, Donohoe D, Webster MW, Lindsley L: Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. Diabetic Ulcer Study Group. *J Amer Coll Surgeons* 183:61–64, 1996
22. Maldonado G, Greenland S: Simulation study of confounder-selection strategies. *Amer J Epidemiol* 138:923–936, 1993
23. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Armstrong DG, Harkless LB, Boulton AJ: 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* 18:133–138, 2001
24. Margolis DJ, Kantor J, Santanna J, Strom BL, Berlin JA: Risk factors for delayed healing of neuropathic diabetic foot ulcers: a pooled analysis. *Arch Dermatol* 136:1531–1535, 2000
25. Margolis DJ, Berlin JA, Strom BL: Risk factors associated with the failure of a venous leg ulcer to heal. *Arch Dermatol* 135:920–926, 1999