Risk Factors for Delayed Healing of Neuropathic Diabetic Foot Ulcers

A Pooled Analysis

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Objective: To estimate the effect of various risk factors on the probability that neuropathic diabetic foot ulcers will heal within 20 weeks of care.

Design and Setting: A pooled or meta-analysis of individual patient data from the standard care arms of 5 randomized clinical trials was conducted. We analyzed 586 subjects with diabetes mellitus who had a neuropathic diabetic foot ulcer. All patients received good wound care, debridement, and “off-loading” of the wound.

Main Outcome Measure: Multivariable logistic regression was used to calculate the magnitude of the association of each risk factor with patients having healed wounds.

Results: Logistic regression odds ratios (ORs; 95% confidence intervals [95% CIs]) revealed that those patients with a diabetic neuropathic foot ulcer that healed within 20 weeks using standard care were more likely to have a smaller wound (OR=0.67; 95% CI, 0.55-0.81), a wound that existed for a shorter period (OR=0.73; 95% CI, 0.61-0.87), and be nonwhite (OR=0.64; 95% CI, 0.43-0.96) compared with patients whose wounds did not heal within 20 weeks. The patient’s age (OR=0.99; 95% CI, 0.89-1.01), serum level of glycosylated hemoglobin at the start of the study (OR=1.03; 95% CI, 0.97-1.10), and sex (OR=1.02; 95% CI, 0.69-1.50) were unassociated with the probability of wound healing. Substantial heterogeneity was not found among the studies.

Conclusions: A standard care regimen for diabetic neuropathic foot ulcers is most likely to be effective for patients who have wounds that are small and of brief duration. This information should help dermatologists decide initially whether to use standard care, to try a new treatment, or to refer the patient to a specialty center.

Arch Dermatol. 2000;136:1531-1535

Foot ulcers and lower extremity amputations are among the most serious complications associated with diabetes mellitus (DM). Lower extremity amputation is more common in persons with DM than in those without DM and affects more than 80,000 persons with DM each year in the United States.1-4 A foot ulcer precedes approximately 85% of lower extremity amputations in patients with DM.5,6 Foot ulcers are present on 2.7% of all patients with DM who are hospitalized.5 Most diabetic foot ulcers are due, at least in part, to loss of cutaneous sensation (peripheral insensate neuropathy), although some of these patients will also have poor arterial flow to their limb.2,3,6 Due to the peripheral neuropathy, patients with DM are unable to perceive sensations, making them vulnerable to trauma.

The Food and Drug Administration (FDA) recently approved a new agent for specifically treating patients with a neuropathic diabetic foot ulcer and adequate lower limb arterial blood flow.7-9 Another agent will, in the near future, be approved by the FDA for this same indication.10 In other words, by virtue of recent advances in the treatment of diabetic foot ulcers, a subset of this ailment, diabetic foot ulcers primarily due to neuropathy can now be treated with new medical therapies. Even with these advances their care usually includes wound debridement, appropriate wound dressings, and “off-loading” the area of the foot that has ulcerated.11-13 Off-loading refers to methods that protect the ulcer from the repetitive trauma of activities of daily living. Off-loading methods include molded shoes, orthotics, crutches, wheelchairs, contact casts, and other devices. Off-loading helps protect the wound so that it can heal. Yet, little has been published on the efficacy of standard care for neuropathic diabetic foot ulcers. Furthermore, to our knowl-
PATIENTS AND METHODS

STUDY IDENTIFICATION AND SELECTION

We previously reported the results of a meta-analysis on the probability that a patient with a diabetic foot ulcer will heal.11 While conducting this study, we realized that approximately 95% of the total number of patients that we identified for the group level meta-analysis were part of a few recently conducted randomized clinical trials. We contacted the industry sponsors of these trials (OrthoMcNeil, Raritan, NJ, and Advanced Tissue Sciences, La Jolla, Calif), both of which agreed to provide us with data and specified variables from the control-arm patients.7-10 All of these studies were randomized phase 2 or phase 3 clinical trials that had been reviewed by the FDA; all were of high quality. These studies used similar criteria to diagnosis neuropathic diabetic foot ulcers, which were that the limbs needed to have adequate arterial perfusion (ie, a transcutaneous oxygen level of >30 mm Hg, or an ankle-brachial index >0.80), and documented foot neuropathy. These patients also received similar care, which included off-loading, debridement, and a moist wound dressing. For these clinical trials, wounds were debrided to remove callous and necrotic tissue. Wounds were often debrided several times during the study. Good wound care included frequent wound cleansing, usually with a saline solution, a moist wound dressing, such as saline-moistened gauze, and the avoidance of topical antiseptics on the wounds. In addition, to ensure that wounds, which were primarily on the forefoot or midfoot, were properly off-loaded several techniques were used. These included molded shoes, half-shoes, crutches, wheelchairs, and bed rest. No sponsoring company was involved, directly or indirectly, in the design or execution of this meta-analysis or in decisions related to the writing or submission of this manuscript.

RISK FACTOR SELECTION AND OUTCOME

Risk factors were selected for evaluation if they had been identified as such in previous publications, and if information about the risk factor was available in all 5 data sets.3,4,14-23 Therefore, as with meta-analyses in general, not all potential interesting risk factors could be evaluated. The patient risk factors we evaluated were as follows: age at the start of the study, sex, ethnicity (white vs all others), serum level of glycated hemoglobin at the start of the study, the area of the wound (in square centimeters) at the start of the study, and the patient’s report of duration (in weeks) of the wound at the start of the study. Data for all 6 of these risk factors were incomplete in all 5 studies. Data on wound duration were unavailable for 102 patients (17%), and data on serum levels of glycated hemoglobin were unavailable for 25 patients (4%). The primary outcome for our analysis was a healed wound within 20 weeks of care. Additional analyses included a healed wound within 12 weeks of care and time to healing.

STATISTICAL ANALYSIS

All analyses used an intention-to-treat approach that included all patients assigned to the standard care arm of each of the 5 studies. Patients who were randomly assigned to the experimental therapy arms were excluded from our analysis even if they actually received standard care.

To calculate the effect of a given risk factor, pooled unadjusted (single-variable) odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using ordinary logistic regression models. Since data on all the risk factors were unavailable for all patients, ORs and 95% CIs are reported separately for all of the patients who had data for each risk factor, and for the patients who had data for all of the risk factors.

The outcomes of interest were modeled using 2 different time end points: patients who healed within 20 weeks of the start of care, and patients who healed within 12 weeks of the start of care. The distributions of both wound area and wound duration were highly skewed. To reduce the influence of large values, the natural logarithms of these variables were used in all models. Each model also included a set of indicator variables representing the study in which each patient had participated. These indicator variables adjusted for variability in the probability of healing across studies that is unexplained by the other risk factors.

Fully adjusted pooled ORs with 95% CIs are also reported. Full adjustment means that the OR for the risk factor of interest is adjusted to consider all of the other risk factors. Since data were unavailable for all of the patients for all risk factors, fully adjusted ORs are reported only for those patients who had complete data for all risk factors. The fully adjusted ORs were also estimated using an imputation algorithm for the missing wound duration data (NORM).24

In the ordinary, or fixed-effects regression approach, the indicator variables allow inferences about the variability in healing rates across the studies included in the analysis. We also constructed random-effects models, which assume that there is a population of studies and that the studies included in our analysis are a random sample from this population.25 This alternative approach can have an effect on the estimated variance of the logistic regression coefficients. The data set was also reanalyzed using a proportional hazards model. The results did not change using the random-effects or proportional hazards models. Therefore, only the ordinary logistic regression (fixed-effects) results are reported.

The heterogeneity of the effect of each variable was assessed using interaction terms between predictors and between each predictor and the study indicator variables. Testing study indicator by risk factor interactions shows whether the association between the risk factor and the probability of healing varies across studies. These interactions were evaluated using the fixed-effects and random-effects models.25-27

To estimate the impact of publication bias, both the Begg test and the Egger publication bias plot were evaluated for all risk factors.28 Neither test gave statistically significant evidence of a publication bias. All analyses were done using SAS software, version 6.12 (SAS Institute Inc, Cary, NC), or Stata, version 5.0, with Stata Technical Bulletin updates (College Station, Tex).
Previously, we conducted a group level meta-analysis to determine the percentage of patients with a neuropathic ulcer that could be expected to heal within 12 or 20 weeks of care. As is often the case, the information available on a group level was insufficient to evaluate risk factors. In the pooled analysis reported here, we use patient level data from the standard care arms of randomized clinical trials that investigated the efficacy of new therapies for the treatment of neuropathic diabetic foot ulcers. Our primary objective was to pool the control arms of several randomized clinical trials to estimate the association of various potential risk factors with the probability that a neuropathic diabetic foot ulcer will heal within 20 weeks of care.

### RESULTS

Aggregating data from the 5 clinical trials, the patients’ mean age was 58 years (age range, 25-93 years). The mean wound size was 1.61 cm² (range, 0.11-111.22 cm²); 94% of the wounds were smaller than 10 cm². The average serum level of glycosylated hemoglobin was 7.5% (range, 3.8%-20.5%). The average wound duration prior to enrollment in the study was 30 weeks (range, 2-1444 weeks). The fraction of men was 73.2%, and 77.8% were white. The fraction of patients who completely healed within 12 weeks of care was 23.9% (95% CI, 20.5%-27.3%). The fraction of men was 73.2%, and 77.8% were white.

The adjusted, risk factor associations that we found for wound healing within 12 and 20 weeks were similar for patients with complete data records and for patients who had incomplete data, with the exception of ethnicity (Table 1). In our analysis of ethnicity, the actual OR for the analysis with imputation was similar to the unadjusted value, 0.69 and 0.64, respectively. However, the P value was not significant when the imputation model was used (P = .09). This, in part, was due to an increased variance produced by the imputation method.

Twenty-week healing rates stratified for 2 risk factor variables, wound size and wound duration, are listed in Table 2. This table clearly shows the association of these 2 variables independently. The bottom third of Table 2 also shows 2 of the 9 possible stratified combinations of wound size and duration on the percentage of patients healed within 20 weeks of care. These combinations are the shorter duration, smaller wound vs the longer duration, larger wound.

Heterogeneity can exist when differences in outcomes are not accounted for by sampling variation. In the analysis of these data, the clinical trial in which the patient was enrolled may be a source of 2 types of heterogeneity. The first type is variability in the probability of healing from clinical trial to clinical trial that is not accounted for by other patient characteristics. To address this type of heterogeneity, fixed-effects and random-effects Q statistics were used. Neither of these approaches led to any statistically significant differences in the model results, and when adjusted for patient characteristics, there was no statistically significant variation in healing rates across studies.

The second type of heterogeneity occurs when the association between patient characteristics and healing varies from clinical trial to clinical trial. Using clinical trial × risk factor interaction terms in the logistic regression models tests this type of heterogeneity. Again, fixed-effects and random-effects models failed to detect any significant heterogeneity, suggesting that the relationship between patient risk factors and healing was constant across studies.

| Table 1. Odds Ratios Comparing Patients Who Healed Within 12 and 20 Weeks* |
|-----------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Factor                      | Total No. In Clinical Trial† | Unadjusted Available Data     | Adjusted: Imputed Data        | Unadjusted: No Missing Data   | Adjusted: No Missing Data    |
| Patients who healed within 12 wk of care |                                |                               |                               |                               |                               |
| Sex, F                      | 586                           | 1.02 (0.66-1.56)               | 1.01 (0.64-1.58)               | 0.93 (0.58-1.51)               | 0.91 (0.54-1.50)               |
| Age, y                      | 586                           | 0.99 (0.97-1.01)               | 0.99 (0.97-1.01)               | 0.99 (0.97-1.00)               | 0.99 (0.97-1.01)               |
| Log duration, wk            | 484                           | 0.73 (0.60-0.89)†              | 0.76 (0.63-0.93)§              | 0.72 (0.59-0.88)§              | 0.78 (0.63-0.95)§              |
| Log area, cm²               | 586                           | 0.62 (0.49-0.77)†              | 0.60 (0.47-0.77)†              | 0.65 (0.51-0.83)§              | 0.62 (0.47-0.82)§              |
| Ethnicity, white            | 586                           | 0.52 (0.34-0.80)§              | 0.56 (0.35-0.89)§              | 0.48 (0.30-0.78)§              | 0.51 (0.30-0.86)§              |
| Hb A1c                      | 561                           | 1.04 (0.98-1.14)               | NE                            | 1.04 (0.98-1.11)               | 0.97 (0.87-1.08)               |

*All values are expressed as odds ratios (95% confidence intervals) unless otherwise stated.
†The sample size is 463 for patients with data for every other variable (ie, complete data) and 586 for the data set containing imputed values of wound duration.
‡P < .005, Wald statistic.
§P < .05, Wald statistic.
||The missing values for the serum level of glycosylated hemoglobin (Hb A1c was not imputed). NE indicates not evaluated.
COMMENT

To our knowledge, this pooled analysis of patient level data is the first analysis of risk factors associated with the healing of neuropathic diabetic foot ulcers to be done using a large sample. We identified 3 predictors of wound healing within 12 or 20 weeks of standard care: the initial wound area, the duration of the wound at the start of treatment, and the patient's ethnicity. Standard care was defined to include debridement, good wound care, and off-loading of the ulcer. Equally important, we found that 3 other factors were not associated with wound healing within 12 or 20 weeks: the patient's age, sex, and serum level of glycosylated hemoglobin measured at the start of care.

Previous assessments of diabetic foot ulcer healing, or lack of healing as represented by a lower extremity amputation, have often concluded that lower limb perfusion is the key risk factor that leads to a poor outcome. These studies had inconsistent reports on the associations of sex, age, ethnicity, wound size, and wound duration with the probability of wound healing. These reports analyzed diabetic foot ulcer of mixed origins.

In our study, we only analyzed patients who were defined objectively as having arterial perfusion of their lower limbs that was adequate for wound healing, and so we did not consider the role of limb arterial perfusion. We used a definition of adequate limb perfusion that was developed in prior studies. We believe that the results of our study and previous studies may differ because the healing associations that we found may have been modified in prior studies by poor limb perfusion. In other words, it is possible that sex, ethnicity, wound size, and wound duration are only associated with wound healing in patients who already have adequate arterial perfusion of their lower limbs and have what can be described as pure neuropathic wounds. Previous investigations may have studied a mix of patients with neuropathic wounds and those with wounds due to arterial insufficiency. Therefore, by design, our results are relevant specifically to patients with DM who have neuropathic foot ulcers and adequate perfusion of their lower limbs. This is the group of patients with DM who had foot ulcers and most likely to respond to nonsurgical care and the group of patients who are the target of the new FDA-approved topical therapies.

There was a remarkable lack of significant heterogeneity in risk factor associations among the studies we analyzed. Therefore, combining all of the study results to obtain estimates of the association between each risk factor and the probability of wound healing is appropriate. The lack of substantial heterogeneity probably relates to the fact that the same sponsor designed many of these studies. Also, all were FDA-reviewed clinical trials. But all of these studies were also multicenter clinical trials. In total, this meta-analysis includes observations made by more than 50 different health care providers (eg, general surgeons, vascular surgeons, dermatologists, internists, primary care physicians, nurses, nurse practitioners, podiatrists, physical therapists). It is therefore likely that this meta-analysis is generalizable to the entire community of health care providers with experience in caring for patients with DM who have neuropathic foot ulcers who use standard care that consists of wound debridement, good wound care, and off-loading of the wound.

Our study has several limitations. We could only evaluate risk factors that were common to all of the clinical trials we included. For example, we did not evaluate associations between wound healing and a patient’s weight, cigarette smoking, type and duration of DM, type of glucose level control, method for off-loading the ulcer, type of wound dressing used on the ulcer, patient compliance, and the influence of comorbid illness. Furthermore, there may have been other large, randomized clinical trials that used a standard care arm that were not published and were not identified when we contacted experts and, therefore, are excluded from our analysis. Since studies that show a positive treatment effect is more likely to be published, publication bias can be an important source of bias when combining studies to estimate the effect of a treatment. However, in our study we evaluated the association of risk factors on wound healing. Treatment benefit, not these associations, was the primary end point of the studies. It is, therefore, doubtful that an association or lack of an association of these risk factors with wound healing would have influenced an author’s decision to publish. In addition, both the Begg test and the Egger bias plot were applied, and neither was consistent with substantial publication bias.

While the effect that this type of publication bias might have had on our results cannot be predicted, we doubt that the effect could have been substantial.

Neuropathic diabetic foot ulcers are often treated in the ambulatory care setting. In fact, the standard-care regimen described in this article can be provided to patients entirely as outpatients. Our meta-analysis of patient level data showed that the use of a standard-care regimen for neuropathic diabetic foot ulcers is most likely to be successful for patients who have more recent (<6 months) and smaller wounds (<2 cm²) (Table 2, bottom third). There also seems to be an influence of ethnicity, in that nonwhite patients do better than white patients. However, there is no biological basis for this finding.

Table 2. Cumulative Healing Rates Within 12 and 20 Weeks of Care for Diabetic Neuropathic Foot Ulcers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample Size, No. (%)†</th>
<th>Healed Within 12 Weeks</th>
<th>Healed Within 20 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound size, cm²</td>
<td>347 (59.2)</td>
<td>29.4 (24.6-34.5)</td>
<td>38.9 (33.8-44.3)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>123 (21.0)</td>
<td>17.9 (11.6-25.8)</td>
<td>25.2 (17.8-33.8)</td>
</tr>
<tr>
<td>2-4</td>
<td>116 (19.8)</td>
<td>13.8 (8.1-21.4)</td>
<td>22.4 (15.2-31.1)</td>
</tr>
<tr>
<td>Wound duration, mo</td>
<td>202 (41.7)</td>
<td>30.2 (24.0-37.0)</td>
<td>41.1 (34.2-48.2)</td>
</tr>
<tr>
<td>&lt;6</td>
<td>88 (18.2)</td>
<td>28.4 (19.3-39.1)</td>
<td>37.5 (27.4-48.5)</td>
</tr>
<tr>
<td>6-12</td>
<td>189 (39.0)</td>
<td>15.3 (10.5-21.3)</td>
<td>23.8 (17.9-30.5)</td>
</tr>
<tr>
<td>Wound size and duration, cm²/mo</td>
<td>120 (24.8)</td>
<td>31.7 (23.5-40.8)</td>
<td>42.5 (33.5-51.8)</td>
</tr>
<tr>
<td>&lt;2/6</td>
<td>52 (12.1)</td>
<td>17.1 (12.6-22.3)</td>
<td>26.2 (20.9-32.1)</td>
</tr>
<tr>
<td>&gt;4/12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients were stratified by wound size, wound duration, and wound size and duration. Except where specified otherwise, all values are expressed as the percentage of healed wounds (exact 95% confidence intervals).† Sample size is reported as the total strata-specific sample (percentage of the total sample).
It is likely that this finding reflects an overall unmeasured bias in the enrollment of patients into these randomized clinical trials (eg, only nonwhites who were perceived to be compliant by the local study investigators were enrolled in these clinical trials). As new treatments for neuropathic diabetic foot ulcers become available, dermatologists and other medical providers should find the risk factor information from this study useful to help them decide whether to use a new treatment in association with standard care, refer to a specialist, or start with standard care alone. Furthermore, when researchers plan future clinical trials for studying nonhealing neuropathic wounds in patients with DM, it is prudent for the investigators to understand these risk factors so that patients who are most likely to fail standard care can be enrolled in the study.

Accepted for publication August 8, 2000.

This study was funded in part by a grant from Curative Health Services to the Trustees of the University of Pennsylvania (Dr Margolis) and by grant AG 00715 from the National Institutes of Health, Bethesda, Md (Dr Margolis).

Sandy Masiak ably provided secretarial support.

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