CHAPTER **15**

PRELIMINARY REPORT OF THE INCIDENCE AND RISKS OF FAILURE TO HEAL FOLLOWING LOWER EXTREMITY AMPUTATION IN NEUROPATHIC DIABETIC PATIENTS

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INTRODUCTION

Neuropathic foot ulcer (Figure 1) and lower extremity amputation (LEA) are common complications of diabetes mellitus (DM). Diabetic individuals suffer 5.5 amputations per 1000 diabetic persons in the United States.[1] In fact, based on data from 2000, in comparison to the overall, unadjusted rate of LEA in the U.S., diabetics are about 19 times more likely to undergo amputation than are persons in the general population (Figures 2, 3). In the 16-year period following 1980, for diabetics, the age-adjusted rate almost doubled, and peaked at 8.2 per 1000 in 1996. In more recent years, a modest decrease in the LEA rate in both the general and diabetic populations has been observed in the U.S. and this, it is speculated, is probably attributable to a combination of educational interventions to enhance awareness, as well as to improvements in medical and surgical treatments of both the ischemic and neuropathic complications of diabetes. Furthermore, approximately $4.6-13.7 billion/year are spent in the U.S. for the treatment of diabetic peripheral neuropathy and its complications, and this accounts for approximately 27% of the direct medical cost of diabetes.[2] Information that allows treating physicians to better understand the risk factors related to the development of diabetic LEA would be useful, and could potentially contribute to a reduction in the incidence of this common complication of DM.

Figure 1.

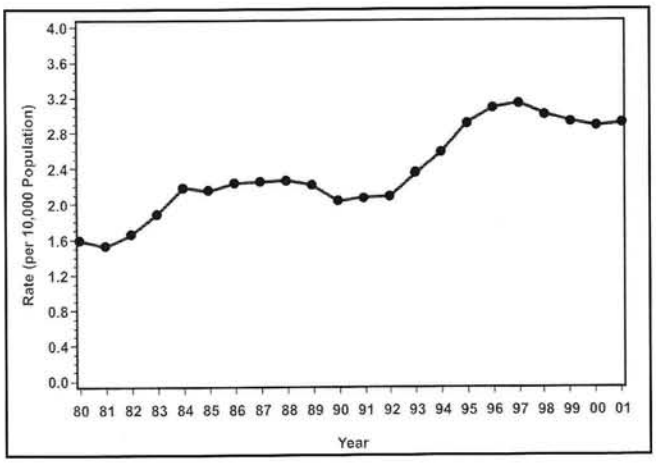

Figure 2.

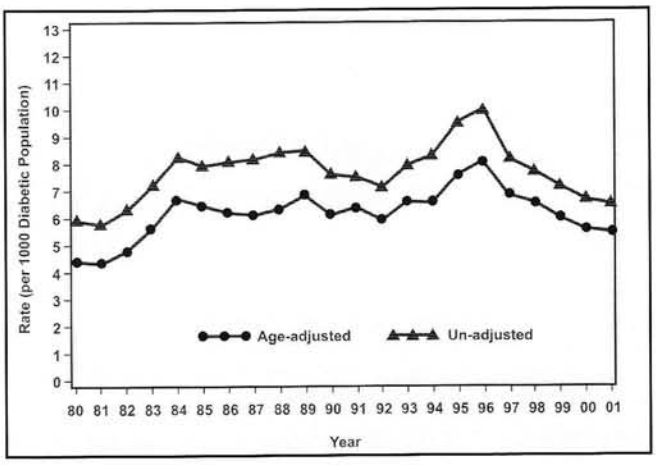

Figure 3.

STUDY AIMS

The primary aim of this study is to determine the incidence of treatment failure (unhealed or ipsilateral second amputation) following LEA in a cohort of neuropathic diabetics who have suffered with previous neuropathic foot ulceration. The secondary aims of this investigation are to identify risk factors associated with failure to heal following LEA in the same cohort of neuropathic diabetic patients seeking wound care at specialized wound care centers in the US. The current investigation, therefore, conveys considerable importance when one considers the fact that the incidence of failure to heal following LEA in diabetic patients is anecdotally reported to be rather high, and a detailed study of the incidence rate and the risk factors associated with such failure has never been critically reported in the literature. Moreover, it will be important to accurately know the incidence of failure to heal following LEA, and to better understand the explanatory risk factors, in order to properly design and power subsequent prospective investigations related to LEA in diabetics.

ETIOLOGY OF ULCERATION AND AMPUTATION, AND STANDARD TREATMENT

Diabetic neuropathic foot ulcer (DNFU) is the hallmark risk factor for subsequent LEA, and is often clinically recognized as subkeratotic hemorrhage affecting the plantar aspect of the foot (Figure 4). It has been shown that peripheral neuropathy is primarily responsible for pedal ulceration in approximately 50% of cases, while arterial insufficiency is primarily responsible for such ulceration in approximately 20% of cases, and combined neuropathy and arterial insufficiency are responsible in approximately 30% of cases.[3,4] For primarily ischemic ulcerations, vascular reconstruction or angioplasty are usually undertaken to improve perfusion of the foot. For the purposes of this study, peripheral neuropathy has been determined to be the main cause of lower extremity ulceration. Specifically, for this cohort, DNFU was defined and confirmed to be a foot ulcers on an individual with loss of protective sensation (LOPS, as determined by failure to sense the 5.10 Semmes-Weinstein monofilament), and adequate ($TCpO2 \geq 30$, ankle-brachial index ≥ 0.8) arterial blood flow to the foot.[5] By using this algorithm, individuals with ischemic ulcers were excluded from the cohort evaluated in this study.

Furthermore, for the purposes of this study, "failure" signifies the composite outcome of either failing to heal or undergoing a second, more proximal ipsilateral amputation following previous LEA. All of the patients in the cohort also underwent standared treatment for their DNFU. Standard treatment of a DNFU consists of debridement, application of a moist dressing, and pressure relief measures (orthoses and shoe gear, total contact casting, Charcot relief orthotics walkers, non-weight bearing ambulation using walking aids or a wheel chair, or bed rest) to off-load the site of cutaneous compromise. The association between wound size and time to healing (Figure 5) has been examined in this same cohort.[5,6] and it has been shown that 65-70% of DNFUs treated standard therapy fail to heal by 20 weeks. With the addition of adjunct treatment measures such as application of platelet-derived growth factors (rhPDGF/

Figure 4A.

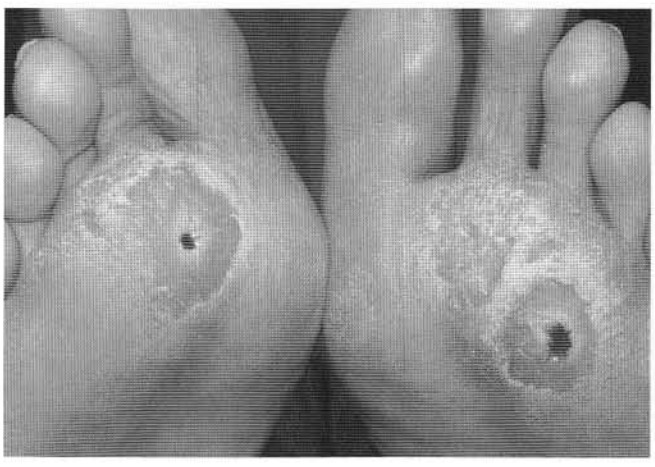

Figure 4B.

Regranex®) and epithelial cell therapies (Apligraf®, Dermagraft®), 50-70% of the DNFUs in this cohort still fail to heal by 20 weeks. Furthermore, deeper wounds have been associated with higher levels of LEAs[7]; and wound size, grade at initial visit predict failure of lower extremity ulcers to heal.[5] Overall, the success rate for healing these wounds is rather abysmal, and a better understanding of the risk factors could be beneficial.

DIABETIC NEUROPATHIC FOOT ULCER AND LOWER EXTREMITY AMPUTATION (LEA)

Margolis and colleagues have shown that the rate of initial LEA (Figure 6) secondary to DNFU is 6.7% (1653 LEAs per 24,616 patients with DNFU), and 63% of those that underwent amputation started with a wound grade ≥ 3 (Table 1), and 46.3% of the LEAs were toe or ray (minor) amputations.[8] These same investigators also showed that approximately 65% of diabetics suffering with a neuropathic foot ulcer will have undergone an initial LEA by 2 months of therapy, approximately 80% will have had an amputation by 3 months, and approximately 90% will have undergone LEA by 4 months (Figure 7). It is also interesting to consider that, in this cohort, the overall percentage of diabetic neuropathic foot ulcers progressing to an initial LEA, by year from before 1991 to 2000, increased gradually (Figure 8) while there was a marked increase in the number of minor (toe or ray) amputations beginning in 1993.

The focus of the current study, however, is to measure the incidence of failure to heal/second LEA (Figures 9, 10) following the initial LEA, in this same cohort. Previous reports of failure to heal following amputation have dealt primarily with major amputations at the below-the-knee level[9], as well as the trans-genicular and above-the-knee levels.[10] These reports deal with case series ranging from 17 to 713 patients, and report second

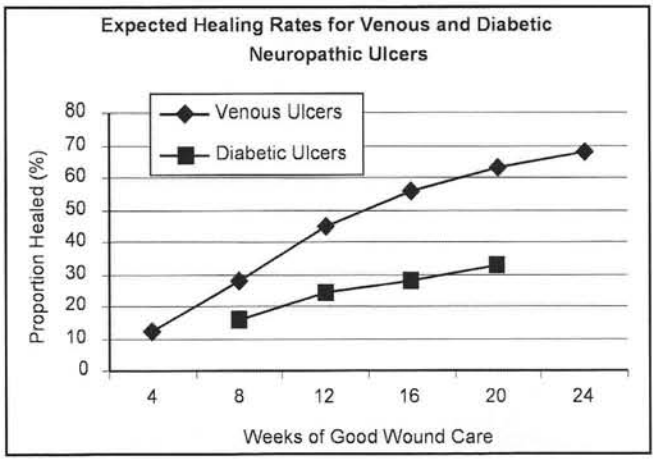

Figure 5.

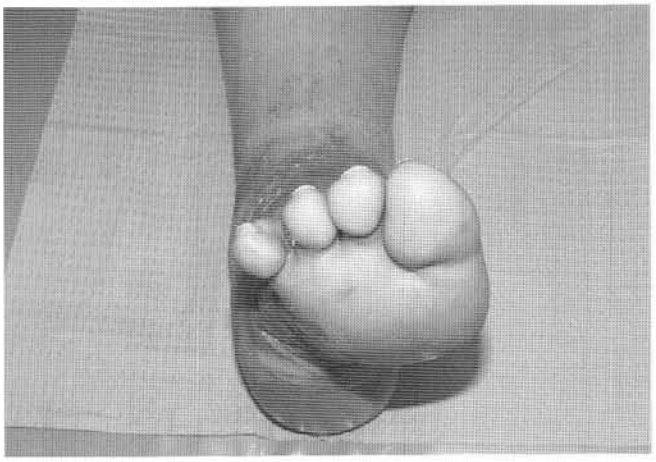

Figure 6.

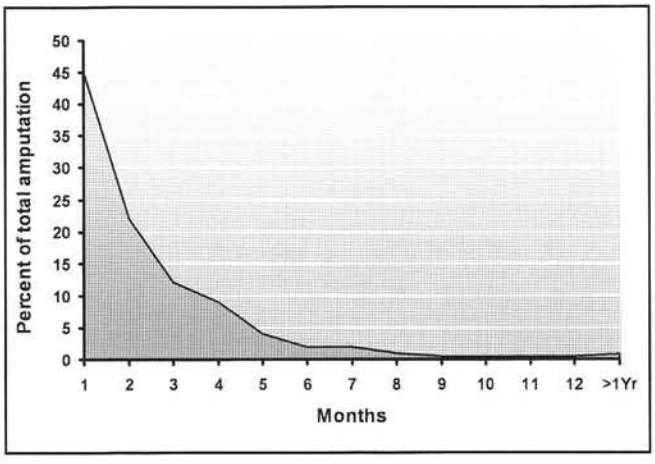

Figure 7.

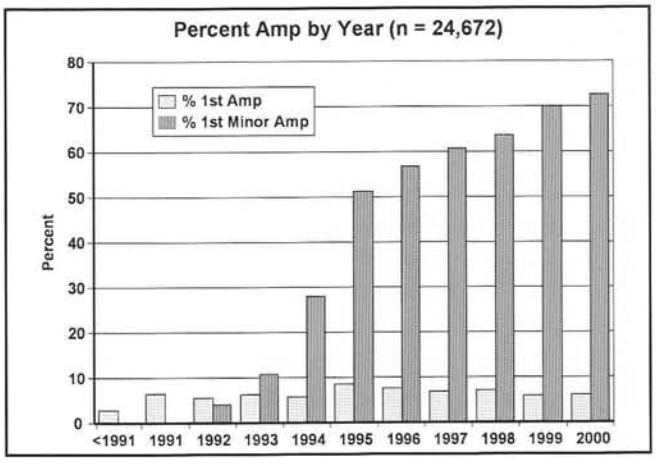

Figure 8.

Table 1

THE CURATIVE HEALTH SERVICES WOUND GRADE CLASSIFICATION

	Wound grade
Grade 1	Partial thickness dermis
Grade 2	Full thickness dermis into subcutaneous fat/superficial fascia
Grade 3	Exposed tendon, ligament, or joint structure
Grade 4	Grade 3 with abscess or osteomyelitis
Grade 5	Grade 3 with necrotic eschar
Grade 6	Gangrene in wound and surrounding tissues

amputation proportions ranging from 18%-32%. These studies, in general, were poorly designed observational reports that dealt primarily with lower extremity critical ischemia.

THE CURATIVE HEALTH SERVICES (CHS) DATASET

Data from *Curative Health Services* network of wound care centers is used for the current study. This network of wound care centers consists of approximately 200 centers, in 38 states, and has been in effect since 1988. All of the patients treated within the wound care system are treated using similar wound care algorithms. To be included in the dataset, a potential subject must have met the following criteria:

- Have a unique identifier in the CHS database;
- Be 18 years of age or older;
- Have had their only, or most recent course of treatment observed in period 1988-2001;
- Have been neuropathic per 10 gram Semmes-Weinstein monofilament;
- Have displayed no significant lower extremity arterial disease (TcPO2, Doppler); and
- Treated for diabetic neuropathic foot ulceration with at least one lower extremity amputation.

Figure 9.

Figure 10A.

Figure 10B.

Basic assessment of the ascertainment criteria for DNFU has previously been performed (n=24,672), and the data has been shown to be valid.[11] In their work, Margolis and colleagues abstracted data from 24,672 records in the dataset, and compared the information with 154 of the medical records for patients with DNFU treated between 1988-1997 in the CHS network. The data were determined to be very accurate (Table 2), and the dataset was shown to be a valuable tool for investigation of outcomes related to DNFU.[12]

STUDY DESIGN

This investigation is a retrospective cohort study using an established and robust dataset consisting of 1775 patients from the Curative Health Services wound care network. All of the patients in the cohort suffered with DNFU prior to undergoing an initial LEA. The primary outcome of interest is failure to heal following the first reported LEA noted in the dataset. Failure to heal is defined as persistence of an amputation stump wound, or undergoing a second, ipsilateral LEA, within 20 weeks following first. From this observation, an estimate of the incidence of failure to heal/second LEA will be made. A wide range of potential risk factors will also be analyzed as independent variables influencing the dependent outcome, and these associations will be considered secondary outcomes. The goal of the investigation is to explain any association between the risk factors and the outcome of interest. The potential risk factors that will be analyzed in this investigation include the following demographic variables:

- Age;
- Sex;
- Insurance coverage (proxy for socioeconomic status);
- CHS center; and
- How the patient was referred to the center.

The following wound related variables will also be analyzed:

- Location;
- Number of wounds;
- Size (mm2) of wound/s;
- Duration (months prior to treatment in CHS);
- Duration (months in CHS up to first LEA);
- Duration (months since first LEA);
- Grade (CHS scale, see Table 1);
- Treatment (GF, cell therapy, HBO); and
- Level of first LEA (AKA, BKA, distal transtibial, hindfoot, transmetatarsal, toe).

Table 2

ASCERTAINMENT OF DNFU (CHS DATASET).

Parameter	Percentage	95% Confidence Interval
% correct	93.4	98.3, 96.8
Kappa	0.86	0.79, 0.91
Sensitivity	0.84	0.72, 0.93
Specificity	0.99	0.94, 0.99
PV(+)	0.98	0.89, 0.99
PV (-)	0.91	0.84, 0.96

Table 3

POWER TABLE (N = 1775, CASES = 657, INCIDENCE = .37, ± = 0.05)

Prevalence of exp	ß when RR=1.5	ß when RR=2	ß when RR=2.5
0.01	0.3685	0.8891	>0.9999
0.05	0.9111	>0.9999	>0.9999
0.1	0.9932	>0.9999	>0.9999
0.15	0.9993	>0.9999	>0.9999
0.2	0.9999	>0.9999	>0.9999
0.25	0.9999	>0.9999	>0.9999
0.33	>0.9999	>0.9999	>0.9999
0.5	>0.9999	>0.9999	>0.9999

The sample size and power to detect a statistically significant difference, in this study, are considered to be very good because of the relatively large sample size. Based on a cohort of 1775 patients undergoing LEA for the management of a DNFU, there are 657 cases of failure to heal following the amputation. Table 3 displays the power for various relative risks based on an incidence rate of 0.37 for failure to heal following an initial amputation for DNFU.

ANALYSIS PLAN

The data will be thoroughly evaluated using descriptive and inferential methods. Risk factors will be characterized by mean and standard deviation for continuous and normally distributed data, and median and quartiles for non-normal distributions. The data will include the following variables:

- Center, and the center's length of experience;
- Patient's age, sex, and insurance category (as a proxy for socioeconomic status);
- Method of referral to the wound care center;
- Wound grade, size (log transformed);
- Number of wounds and their locations;
- Duration of wound (log transformed);
- Prior and adjunct treatment (hyperbaric oxygenation, platelet releaseate, cell therapies); and
- Level of amputation (minor or major LEA).

Estimates of association will be computed using chi-square statistics, one-way analysis of variance (ANOVA), and univariable Kaplan-Meier curves will be made for failure to heal and second LEA. Furthermore, multi-variable logistic regression will be used to estimate the magnitude of effect of any given explanatory variable, and Cox proportional hazards models will be constructed to make inferences related to the time to failure/second LEA. Fixed effects models and models allowing variability among centers using generalized estimating equations will also be constructed. We will also perform polychotomous (multinomial) pairwise comparisons, including healed versus unhealed, and unhealed versus second LEA. Associations will be reported using the point estimate in terms of the odds ratio with a 95% confidence interval for unadjusted and fully adjusted models. Finally, Greenland and Rosenbaum sensitivity analyses will be performed in an effort to determine the degree to which unmeasured confounders may influence our results.

PRELIMINARY RESULTS

To date, the data has been refined and made free of inconsistencies, and work has begun in an effort to formulate the explanatory model for failed amputation. So far, only the unadjusted incidence of failure/second LEA has been calculated. The incidence was calculated to be 37% (1775 in cohort, 1118 healed LEAs, 657 failed to heal). Of the 657 failed LEAs, 81% were observed by 120 days, 90% by 130 days, and 96% by 140 days, following the first amputation. As expected, the percentage of second amputations that are considered minor (toe or ray) is notably less than the percentage of initial amputations that are considered minor (Table 4).

Table 4

INITIAL AND SECOND LEAS, AND DESIGNATION AS A "MINOR" AMPUTATION, BY YEAR.

Year	% Amp	% Minor Amp	% 2nd Amp	% Minor 2nd Amp
<1991	2.79	0	28.44	0
1991	6.3	0	31.3	0
1992	5.55	4	29.87	1
1993	6.24	10.71	36.77	3.2
1994	5.62	28	46.21	2.3
1995	8.4	51.24	43.27	4.5

LIMITATIONS OF THIS INVESTIGATION

The potential limitations of this retrospective cohort study include the generalizability of dataset:

- Possibly only generalizes to patients seen within the CHS system, although this is not likely in light of the large sample size and wide geographic distribution;
- Referral patterns to the wound care centers; and
- Ambulatory, outpatient population (more forefoot cases, and probably less hindfoot and ankle, and decubitus lesions).
- Moreover, there is always the risk of confounding by unobserved variables, such as:
- Smoking status, body mass index (BMI), foot type, ankle range of motion, plantar foot pressure;
- Renal disease, retinopathy, cerebral; vascular disease, coronary artery disease, infection; and
- TcPO2, clinical vascular measurements, HbA1c, albumin, etc.

It is possible that any of these variables may influence the likelihood of failure to heal following a first LEA. As with prior use of this dataset, we will also perform Greenland and Rosenbaum sensitivity analyses to determine the robust nature of our inferences in the presence of unmeasured potential confounders.

FUTURE DIRECTIONS

After completion of this explanatory investigation, we would like to develop predictive models and formulate guidelines for surgeons to avoid the failed first amputation. Moreover, we would like to conduct a properly designed prospective cohort study, controlling for a wide range of independent variable, including:

- DNFU; followed over time (5 years), and look at time-to-event analysis for different outcomes and costs of care

QUALITY OF LIFE MEASUREMENTS

Outcomes: failure to heal, second ipsilateral and/or contralateral LEA

- Vascular data (ABI, TcPO2), comorbidity status (nutrition, CAD, CVA, ESRD, smoking, infection), family history, compliance with therapeutic regimens, foot type/deformities and pressure measurements, ranges of motion, BMI, activity level, pertinent labs (HbA1c, albumin, etc.), self-reported race and ethnicity
- Level of first amputation, using a yet-to-be developed, reliable instrument for determining, in a valid fashion, the "best" level for the first LEA in this population

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