Factors Associated With Lower-Extremity Amputation in Patients With Diabetic Foot Ulcers

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ABSTRACT

Objective: To explore factors associated with lower-extremity amputation (LEA) in patients with diabetic foot ulcers using data from the Online Wound Electronic Medical Record Database.

Design: Retrospective analysis of medical records.

Setting and participants: Data from 169 individuals with previously diagnosed diabetes mellitus who received wound care for a 6-month period within a span of 2 years was analyzed. A baseline evaluation was obtained and wound(s) were treated, managed, and monitored. Treatment continued until the patient healed, required an LEA, or phased out of the study, neither healing nor undergoing an amputation. Of the 149 patients who completed the study, 38 had healed ulcers, 14 underwent amputation, and 97 neither healed nor underwent an amputation. All patients were treated under the care of vascular and/or podiatric surgeons.

Measurements: Variables included wound status (healed, amputated, and unhealed/non-amputated); size of wound area; age, gender, race, and ethnicity; white blood cell (WBC) count, hemoglobin A1c (HbA1c), blood glucose, and body mass index (BMI); and presence of osteomyelitis, gangrene, and peripheral vascular disease.

Results: As compared to the healed and unhealed/non-amputated group, the group of patients who underwent LEA was older and had higher percentages of males, Hispanics, and African Americans; had a higher WBC count, larger wound area, and higher rates of wound infection, osteomyelitis, and neuropathy; and had lower average values of HbA1c, blood glucose, and BMI and a lower rate of peripheral vascular disease.

Conclusion: The association between HbA1c and LEA highlights a window of relative safety among an at-risk population. By identifying and focusing on factors associated with LEA, health care professionals may be able to decrease the prevalence of LEA in patients with diabetes.

Keywords: diabetic foot ulcer; lower-extremity amputation; risk factors; HbA1c.

An estimated 30.3 million people, or 9.4% of the US population, has diabetes. In 2014, approximately 108,000 amputations were performed on adults with diagnosed diabetes.[1] Furthermore, patients with diabetes have a 10-fold increased risk for lower-extremity amputation (LEA), as compared with patients without diabetes.[2] The frequency of amputations in the diabetic population is a public health crisis.

Amputation has significant, life-altering consequences. Patients who undergo LEA often face debilitation in their daily activities and must undergo intense rehabilitation to learn basic tasks. Amputations can also impact individuals' psychological well-being as they come to terms with their altered body and may face challenges in self-perception, confidence, self-esteem, work life, and relationships. In addition, the mortality rate for patients with diabetes 5 years after undergoing LEA is 30%.[2] However, public health studies estimate that more than half of LEAs in patients with diabetes are preventable.[3]

Although studies have explored the relationship between diabetes and LEA, few have sought to identify factors directly correlated with wound care. In the United States, patients with diabetic ulcerations are typically treated in wound care facilities; however, previous studies have concentrated on the conditions that lead to the formation of an ulcer or amputation, viewing amputation and

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ulcer as 2 separate entities. Our study took into account systemic variables, patient demographics, and specific wound characteristics to explore factors associated with LEA in a high-risk group of patients with diabetes. This study was designed to assess ailments that are prevalent in patients who require a LEA.

Methods

Patients and Setting

A total of 169 patients who were treated at the Comprehensive Wound Healing and Hyperbaric Center (Lake Success, NY), a tertiary facility of the Northwell Health system, participated in this retrospective study. The data for this study were obtained in conjunction with the development of the New York University School of Medicine's Online Wound Electronic Medical Record to Decrease Limb Amputations in Persons with Diabetes (OWEMR) database. The OWEMR collects individual patient data from satellite locations across the country. Using this database, researchers can analyze similarities and differences between patients who undergo LEA.

This study utilized patient data specific to the Northwell Health facility. All of the patients in our study were enrolled under the criteria of the OWEMR database. In order to be included in the OWEMR database, patients had to be diagnosed with type 1 or type 2 diabetes; have a break in the skin ≥ 0.5 cm^2; be 18 years of age or older; and have a measured hemoglobin A1c (HbA1c) value within the past 120 days. Study patients signed an informed consent and committed to being available for follow-up visits to the wound care facility for 6 months after entering the study. Patients were enrolled between 2012 and 2014, and each patient was monitored for a period of 6 months within this time period. Participants were treated with current standards of care using diet, lifestyle, and pharmacologic interventions. This study was approved by the Northwell Health System Institutional Review Board Human Research Protection Program (Manhasset, NY).

Data Collection

On their first visit to the facility, patients were given a physical examination and initial interview regarding their medical history. Clinicians were required to select 1 ulcer that would be examined for the duration of the study. The selection of the ulcer was based on a point system that awarded points for pedal pulses, the ability to be probed to the bone, the location of the ulcer (ie, located on the foot rather than a toe), and the presence of multiple ulcerations. The ulcer with the highest score was selected for the study. If numerous ulcers were evaluated with the same score, the largest and deepest was selected. Wagner classification of the wound was recorded at baseline and taken at each subsequent patient visit. In addition, peripheral sensation was assessed for signs of neuropathy using Semmes-Weinstein monofilament testing.

Once selected, the wound was clinically evaluated, samples for culture were obtained, and blood tests were performed to detect the presence of wound infection. The patient's blood was drawn for a full laboratory analysis, including white blood cell (WBC) count and measurement of blood glucose and HbA1c levels. Bone biopsy, magnetic resonance imaging, and bone scans were used to detect the presence of osteomyelitis at the discretion of the health care provider. Wounds suspected of infection, underlying osteomyelitis, or gangrene at baseline were excluded. Patients would then return for follow-up visits at least once every 6 weeks, plus or minus 2 weeks, for a maximum of 6 months.

Statistical Analysis

Utilizing SAS version 9.3 (Cary, NC), descriptive statistics (minimum, maximum, mean, median, and SD) were calculated for the following variables: age, WBC count, wound area, HbA1c, blood glucose, and body mass index (BMI). These variables were collected for each patient as per the OWEMR protocol and provided a basis for which to compare patients who underwent amputation and those who did not. Twenty patients were lost to follow-up, and therefore we altered the window of our statistics from 6 months to 3 months to provide the most accurate data, as 6-month follow-up data were limited. The patients were classified into the following categories: healed, amputated, and unhealed/non-amputated. Descriptive statistics were calculated for these 3 groups, analyzing the same variables (age, WBC count, wound area, HbA1c, blood glucose, and BMI). Additional statistical computations were utilized in order to show the prevalence and frequency of our categorical variables: gender, race, ethnicity, osteo-

Table 1. **Descriptive Statistics of Study Patients**

Variable	No. of Patients	No. With Missing Data	Mean (SD)	Median	Minimum	Maximum
Age, yr	169	0	62.57 (13.23)	63.00	27.00	90.00
WBC count, cells × 10^3/µL	163	6	9.61 (4.40)	8.70	2.90	34.00
Wound area, cm^2	169	0	12.97 (19.76)	4.00	0.50	96.99
HbA1c, %	168	1	8.49 (2.16)	8.10	5.10	16.30
Blood glucose, mg/dL	161	8	166.19 (86.60)	145.00	44.00	521.00
BMI	130	39	31.22 (6.81)	30.37	19.72	51.00

BMI, body mass index; HbA1c, hemoglobin A1c; WBC, white blood cell.

myelitis, gangrene, and peripheral vascular disease. The baseline values of WBC count, HbA1c, wound area, and BMI of the 3 groups were analyzed with descriptive statistics for comparison. A multinomial logistic regression was then performed using a 3-level outcome variable: healed, amputated, or unhealed/non-amputated. Each predictor variable was analyzed independently due to the small sample size.

Results

Of the 169 registered patients treated at the Northwell Health facility, all qualified for the OWEMR study and met the study criteria. In the original 169 patients, there were 19 amputations: 6 toe, 6 trans-metatarsal, 6 below knee, and 1 above knee (**Table 1**). The descriptive statistics of 149 patients grouped into 3 categories (healed, amputated, unhealed/non-amputated) are shown in **Table 2**.

The results of the logistic regression exploring the differences between the amputation and healed groups and the unhealed/non-amputated group are shown in **Table 3**. The amputation group had a higher mean age and WBC count and greater wound area. Increased age was determined to be a significant predictor of the odds of amputation (P = 0.0089). For each year increase in age, the odds of amputation increased by 6.5% (odds ratio, 1.07 [95% confidence interval {CI}, 1.02-1.12]). Patients in the amputation group were more likely to be male, Hispanic, and African American and to have wound infections and comorbidities (osteomyelitis, neuropathy, and gangrene).

The presence of gangrene was significantly associated with LEA (P = 0.03). Specifically, the odds of patients without gangrene undergoing a LEA were substantially lower compared with their counterparts with gangrene (odds ratio, 0.17; 95% CI, 0.04-0.68; P = 0.0131). However, the presence of gangrene was not associated with the odds of healing compared with the odds of neither healing nor undergoing amputation (P = 0.84; not shown in Table 3).

The amputation group had lower mean values for HbA1c, BMI, and blood glucose levels and a lower rate of peripheral vascular disease. Only the relationship between lower HbA1c and increased odds of amputation versus not healing/non-amputation was found to be statistically significant (95% CI, 0.27-0.78; P = 0.009).

Discussion

This retrospective study was undertaken to evaluate factors associated with LEA in patients with diabetic foot ulcers. Patients with diabetes being treated at a wound care facility often require continuous surgical and metabolic intervention to promote optimal healing: drainage, surgical debridement, irrigation, culturing for infection, and monitoring of blood glucose levels. This treatment requires strict compliance with medical directions and, oftentimes, additional care, such as home-care nursing visits, to maintain a curative environment for the wound. Frequently, wounds on the lower extremity further complicate the healing process by reducing the patient's mobility and daily life. Due to these factors, many patients progress to LEA. The link between diabetic ulcers and amputation has already been well described in previous studies, with studies showing that history of diabetic foot ulcer significantly

Table 2. **Characteristics of Patients at 3-Month Follow-up**

Characteristic	Unhealed/Non-amputated (n = 97)	Healed (n = 38)	Amputated (n = 14)
Demographics			
Sex, no. (%)			
Male	81 (84)	26 (68)	10 (71)
Female	16 (16)	12 (32)	4 (29)
Race, no. (%)			
Asian	3 (3)	0 (0)	0 (0)
Black	22 (23)	7 (18)	4 (29)
White	62 (64)	27 (71)	9 (64)
Other	10 (10)	4 (11)	1 (7)
Ethnicity, no. (%)			
Hispanic	5 (5)	4 (11)	2 (14)
Non-Hispanic	92 (95)	34 (89)	12 (86)
Age, mean (SD), yr	61.97 (13.32)	62.63 (12.90)	72.21 (12.25)
Comorbidities, no. (%)			
PVD[a]	25 (27)	6 (16)	1 (8)
OM	30 (31)	12 (32)	8 (57)
Neuropathy	92 (95)	31 (82)	14 (100)
Gangrene	6 (6)	2 (5)	4 (29)
Wound assessments			
Wound infection, no. (%)	36 (37)	15 (39)	9 (64)
Wound area, mean (SD), cm^2	16.60 (23.12)	7.60 (15.42)	11.78 (9.68)
Laboratory results			
Hemoglobin A1c, mean (SD), %	8.43 (2.04)	8.75 (2.12)	6.77 (0.82)
No.	96	38	14
Blood glucose, mean, mg/dL	158.40 (78.06)	163.19 (84.43)	149.29 (55.97)
No.	90	37	14
WBC count, mean (SD), cells × 10^3/µL	9.64 (4.12)	9.26 (3.88)	9.68 (4.63)
No.	92	37	14
BMI, mean (SD)	30.65 (5.98)	31.44 (8.53)	28.98 (6.39)
No.	73	31	11

BMI, body mass index; OM, osteomyelitis; PVD, peripheral vascular disease; WBC, white blood cell.
[a]For amputated group, n =13.

predisposes an individual to LEA.[4] However, few studies have further investigated demographic factors associated with risk for an amputation. Our study analyzed several categories of patient data taken from a baseline visit. We found that those with highly elevated HbA1c values were less likely to have an amputation than persons with relatively lower levels, a finding that is contrary to previous studies.

Our study's findings suggest a higher risk for LEA with increased age. The amputation group was, on average, 7 years older than the other 2 groups. A recent study showed that risk for amputation is directly correlated to patient age, as is the mortality rate after undergoing LEA (2.3%; $P < 0.05$).[5] Our study found that with each increase in age of 1 year, the odds of amputation increased by 6.5%. However, recent evidence on LEA risk and aging

Table 3. **Results of Multinomial Logistic Regression Examining Differences Between Amputation Versus Unhealed/Non-amputated Groups and Healed Versus Unhealed/Non-amputated Groups (n = 149)**

	Wald χ^2	*P* Value	Amputation Group[a] OR (95% CI)	Healed Group[a] OR (95% CI)
Demographics				
Sex (ref. female)	4.03	0.13	0.49 (0.14-1.77)	0.43 (0.18-1.02)
Race (ref. white)	1.21	0.88		
Black			1.25 (0.35-4.48)	0.73 (0.28-1.91)
Others			0.53 (0.06-4.55)	0.71 (0.21-2.37)
Hispanic (ref. non-Hispanic)	2.10	0.35	3.07 (0.54-17.59)	2.17 (0.55-8.54)
Age	6.89	0.03[b]	1.07 (1.02-1.12)	1.00 (0.98-1.03)
Comorbidities				
No OM (ref. presence of OM)	3.60	0.17	0.34 (0.11-1.05)	0.97 (0.43-2.18)
No PVD (ref. presence of PVD)[c]	3.28	0.19	4.35 (0.54-35.18)	1.93 (0.72-5.17)
No gangrene (ref. presence of gangrene)	7.10	0.03[b]	0.17 (0.04-0.68)	1.19 (0.23-6.16)
Wound assessments				
No infection (ref. presence of infection)	3.51	0.17	0.33 (0.10-1.06)	0.91 (0.42-1.95)
Wound area	4.62	0.10	0.99 (0.96-1.02)	0.97 (0.94-1.00)
Laboratory results				
Hemoglobin A1c[c]	9.46	0.009[b]	0.46 (0.27-0.78)	1.08 (0.90-1.29)
Blood glucose[c]	0.33	0.85	1.00 (0.99-1.01)	1.00 (1.00-1.01)
WBC[c]	0.25	0.88	1.00 (0.88-1.15)	0.98 (0.89-1.08)
BMI[c]	1.08	0.58	0.96 (0.87-1.07)	1.02 (0.96-1.08)

Note: Variable in parentheses is the reference category.

BMI, body mass index; OM, osteomyelitis; OR, odds ratio; PVD, peripheral vascular disease; WBC, white blood cell.

[a] No amputation/unhealed group is the reference category.
[b] Amputation versus no amputation/unhealed group odds ratio, $P < 0.05$.
[c] Variables with smaller sample sizes: n = 145 for PVD, n = 148 for HbA1c, n = 141 for blood glucose, n = 143 for WBC, n = 115 for BMI.

suggests that age is of less consequence than the duration of diabetes. One study found that the propensity to develop diabetic foot ulcers increases with the duration of diabetes.[6] The same study found that prevalence of ulceration was correlated with age, but the relationship between age and LEA was less significant. A follow-up study for LEA could be done to examine the role of disease duration versus age in LEA.

A consensus among previous studies is that men have a higher risk for LEA.[5,7] Men comprised the majority in all 3 groups in our study. In addition, the amputation group in our study had the lowest BMI. Higher BMI generally is associated with an increased risk for health complications. However, a past study conducted in Taiwan reported that obese patients with diabetes were less likely to undergo LEA than those within the normal range for BMI.[8] Neither study suggests that obesity is a deterrent for LEA, but both studies may suggest that risk of amputation may approach a maximum frequency at a specific BMI range, and then decrease. This unconfirmed "cyclic" relationship should be evaluated further in a larger sample size.

Most patients in our analysis were Caucasian, followed by African American and South Asian. African Americans were the only racial group with an increased frequency in the amputation group. This finding is supported by a previous study that found that the rate of LEA among patients with diabetes in low-income, predominantly African-American neighborhoods was nearly double that in wealthier, predominantly Caucasian areas.[9] A potential problem in the comparison between our data with previous studies is that the studies did not analyze patients with our inclusion criteria. All patients with diabetes in previous investigations were grouped by race, but were not necessarily required to have 1 or more ulcers. Multiple ulcers may predispose an individual to a greater risk for amputation.

Multinomial logistic regression did not suggest an association between initial size of a patient's wound and the risk of amputation. However, the descriptive data suggests a trend. Patients who did not heal or require an amputation had the largest average wound area. This finding is not surprising in that our study followed individuals for only 3 months. Many wounds require a long course of treatment, especially in patients with diabetes, who may have poor vascularization. However, in comparison to the healed patients, the patients who required an amputation had a larger average wound area. A larger wound requires a plentiful vascular supply for the delivery of clotting factors and nutrients to the damaged area. As wound size increases, an individual's body must transmit an increased quantity of these factors and nutrients for the regeneration of tissue. In addition, wounds that possess a larger surface area require more debridement and present a greater opportunity for infection. This may also foreshadow a longer, more costly course of treatment. Additionally, individuals coping with large ulcerations are burdened by more elaborate and complex wound dressings.

Elevated levels of HbA1c are associated with increased adverse effects of diabetes, including end-stage renal disease, neuropathy, and infection.[10] In a previous study, the risk for amputation was 1.2 times higher in patients with elevated HbA1c.[11] In contrast, our study suggested the odds of LEA versus not healing/not undergoing amputation decreased as HbA1c increased. As a patient's HbA1c level increased by a value of 1, their odds for LEA decreased by 54.3%. This finding contradicts prior studies that have found a positive association between HbA1c and LEA risk, including a study where each percentage increase in HbA1c correlated with a 13% to 15% increased risk of LEA.[12] The finding that patients who underwent amputation in our study had lower levels of HbA1c and blood glucose cannot be fully explained. The maximum HbA1c value in the amputated group was 7.9%. The average values for healed patients and those who underwent LEA were 8.75% and 6.77%, respectively.

Blood glucose levels were also found to be the lowest in the amputated group in our study (mean, 149.29 mg/dL vs 163.19 mg/dL in the healed group). Similar results were found in a Brazilian study, in which patients who did not require amputation had higher HbA1c levels. This study also found an association between blood glucose levels above 200 mg/dL and amputations.[3] These findings provide interesting opportunities for repeat studies, preferably with a larger number of participants.

Our study is limited by the small sample size. The sample population had to be reduced, as many patients were lost to follow-up. Although this paring down of the sample size can introduce bias, we are confident that our study is representative of the demographic of patients treated in our facility. The loss of patients to follow-up in turn caused the window of analysis to be narrowed, as long-term outcome data were not available. A multisite study observing various population samples can better explore the relationship between HbA1c and risk of amputation.

Conclusion

This retrospective study exploring factors associated with LEA was unique in that all our participants had 1 or more diabetic foot ulcerations, and thus already had an extremely high risk for amputation, in contrast to previous studies that followed persons at risk for developing diabetic foot ulcerations. In contrast to several previous studies, we found that the risk for amputation actually decreased as baseline measurements of HbA1c increased. The results of this study offer many opportunities for future investigations, preferably with a larger sample size. By further isolating and scrutinizing specific factors associated with LEA, researchers can help clinicians focus on providing wound care that promotes limb salvage.

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