Neuropathy May Be an Independent Risk Factor for Amputation After Lower-Extremity Burn in Adults With Diabetes

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IN BRIEF Treatment of lower-extremity burn injuries in adults with diabetes can be complex, and some diabetes-related factors can lead to impaired healing of such wounds, putting patients at risk of amputation. In this retrospective review of adult patients with lower-extremity burns, patients with pre-injury neuropathy and higher A1C levels were more likely to require amputations after their burn injury. The authors conclude that lower-extremity burn injuries in patients with diabetes require close follow-up and possibly referral to a burn specialist for interventions and treatment strategies to offset more serious complications.

For patients with diabetes, lower-extremity burn wounds can be a significant and morbid medical problem (1,2). Patients with diabetes have a significant risk of poor wound healing, and severe burn injury to lower extremities can result in the loss of toes or legs (3). However, diabetes has a large spectrum of severity and complications. Long-standing and severe complications such as microvascular disease and neuropathy complicate wound healing and may significantly increase the risk of limb amputation (4). Poor long-term glycemic control may also significantly affect wound healing and increase amputation risks (5).

Our previous work (6) highlighted the risks that patients with diabetes can suffer from a burn injury. These burn injuries were relatively small but resulted in significant morbidity. Additionally, many of the burn injuries suffered by patients with diabetes are caused by patients using heating or warming devices (e.g., heating pads or hot water bottles) to relieve pain and discomfort in their feet and legs (6). These injuries may be preventable through patient and provider education about not only burn injury risks from prolonged use of heating and warming devices, but also potential risk of amputations from nonhealing burn wounds (7).

Here, we report on a study seeking to further elucidate the risk of amputation in patients with diabetes who have suffered a burn injury, to foster education and burn prevention for high-risk patients. We hypothesized that poor long-term glucose control and development of diabetes-associated neuropathy increases the risk of amputation after a burn injury. Our aim for this study was to analyze the incidence of lower-extremity amputation of burned limbs of patients with diabetes and determine diabetes-related factors associated with this outcome.

Methods

We performed an 11-year retrospective review of adult patients admitted to our burn unit. Before initiating this study, we obtained regulatory approval from the University of California Davis institutional review board. We used patient electronic medical records and our local burn unit patient

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https://doi.org/10.2337/cd18-0066

registry to identify patients. Inclusion criteria were age ≥18 years, lower-extremity burn injury, and a history of diabetes. We excluded all patients who were transitioned to palliative care and deemed to have a nonsurvivable burn injury on admission by the treating burn surgeon.

We collected data on the following clinical variables: age, sex, medical history, surgical history, home medications, presence or history of neuropathy on admission, smoking status, ethnicity, total body surface area (TBSA) burned, admission blood glucose, admission A1C, admission renal function analysis, length of hospital stay, number of operations, and amputation of lower-extremity during hospitalization. The treating burn surgeon directed all treatment. Decisions regarding amputation of the affected limb during hospitalization were also made by the treating burn surgeon.

R statistical software (the R Foundation, www.r-project.org) was used to analyze collected data. A Wilks-Shapiro test was used to test for normality of the data. For normally distributed continuous data, Student's *t* test was used to test for the difference between means of amputation patients (AMP) and no-amputation patients (no-AMP). For data that were not normally distributed, the Wilcoxon rank sum test was used to determine differences between means. Fisher's exact test was used to test for differences between categorical data. Multivariate logistic regression analysis was used to identify independent admission patient risk factors for amputations after a lower-extremity burn injury. All mean values are reported as mean ± SD and all median values are reported as median (interquartile range [IQR]). A significance value of $P < 0.05$ was set to determine statistically significant results.

Results

A total of 113 patients were included in the study. All had type 2 diabetes. Men made up the overwhelming majority of the patients (80%). The mean age 56 ± 14 years, and the median TBSA was 3.5% (IQR 2–10). Noninsulin diabetes medications were used by 36% of patients, insulin alone was used by 49%, and 15% of the patients did not use any medications for glucose control. Eighteen percent of patients had a history of a previous lower-extremity amputation, and 56% had a preexisting diagnosis of diabetic neuropathy on admission. Mean admission blood glucose was 212 ± 107 mg/dL, mean admission A1C was 8.8 ± 2.5%, mean admission blood urea nitrogen (BUN) was 21 ± 15 mg/dL, and median creatinine (CR) was 0.96 mg/dL (IQR 0.75–1.5). The median number of operations was 1 (IQR 0–2), and the median length of hospital stay was 13 days (IQR 8–22) (Table 1). In total, 16% of patients required a lower-extremity amputation of the burned limb after admission. Of these amputations, 10 were below-knee amputations, 1 was an above-knee amputation, 4 were trans-metatarsal amputations, and 3 were amputations of the toes.

We divided the patients into two groups: those who required a lower-extremity amputation after a burn injury (AMP) and those who did not (no-AMP). There was no significant difference in the proportion of patients who had a previous amputation between no-AMP and AMP (18 vs. 17%). There was also no significant difference in mean age (58 ± 14 vs. 53 ± 12 years, $P = 0.69$) or median TBSA burned (4% [IQR 2–10] vs. 2.3% [IQR 1.3–3.4], $P = 0.4$) between no-AMP and AMP.

We analyzed for differences in patient characteristics between the two groups (Table 2). Noninsulin diabetes medications were used by 38% in the no-AMP group and

TABLE 1. Admission Demographics and Variables

Patients, *n*	113
Men, *n*	90
Women, *n*	23
Mean age, years	56 ± 14
Race/ethnicity, %	
White	52
Asian	23
Black	8
Other	15
Current smoker, %	25
Using noninsulin diabetes medication, %	36
Using insulin, %	49
Using no diabetes medication, %	15
Pre-injury amputation, %	18
History of neuropathy, %	56
Median TBSA burned, %	3.5 (IQR 2–10)
Median length of hospital stay, days	13 (IQR 8–22)
Mean admission blood glucose, mg/dL	212 ± 107
Mean admission A1C, %	8.8 ± 2.5
Mean admission BUN, mg/dL	21 ± 15
Median admission CR, mg/dL	0.96 (IQR 0.75–1.5)

All mean values are expressed as mean ± SD. All median values are expressed as median (IQR).

TABLE 2. Comparison of Demographics and Variables Between AMP and no-AMP Patient Groups

Variable	No-AMP Group	AMP Group	*P*
Mean age, years	58 ± 14	53 ± 12	0.17
Median TBSA burned, %	4 (2–10)	2.25 (1.25–3.4)	0.4
Current smoker, %	25	28	0.77
Pre-injury amputation, %	7.5	16.7	1.0
Using noninsulin diabetes medication, %	38	28	0.6
Using insulin, %	46	61	0.6
Using no diabetes medication, %	16	11	0.6
Mean admission blood glucose, mg/dL	209 ± 101	213 ± 13	0.87
Mean admission A1C, %	8.6 ± 2.5	10 ± 2.4	0.04
History of neuropathy, %	49	89	0.002
Mean admission BUN, mg/dL	21 ± 15	19 ± 13	0.65
Median admission CR, mg/dL	0.97 (0.8–1.5)	0.84 (0.6–2.4)	0.53

All mean values are expressed as mean ± SD. All median values are expressed as median (IQR).

28% in the AMP group; 46% of the no-AMP group and 61% of the AMP group used insulin only; and 16% of no-AMP and 11% of AMP patients did not use any medication for diabetes control. Overall, there was no difference in the type of medication used for diabetes control (P = 0.61). Neuropathy was present on admission in 49% of no-AMP patients; however, 89% of patients in the AMP group had neuropathy present on admission (P = 0.002). Admission blood glucose did not significantly differ between the groups (209 ± 101 vs. 213 ± 138 mg/dL). However, A1C was significantly different; mean admission A1C was 8.6 ± 2.5% in the no-AMP group and 10 ± 2.4% in the AMP group (P = 0.04). There was no difference in mean admission BUN (21 ± 15 vs. 19 ± 13 mg/dL, P = 0.65) or median admission CR (0.97 [IQR 0.8–1.5] vs. 0.84 [IQR 0.6–2.4 mg/dl], P = 0.53).

We created a multivariate model based on admission variables to determine independent risk factors for amputation. Using a step-wise subtraction method based on lowest Akaike Information Criterion, the best-fit model comprised the following variables: TBSA burned, A1C, current smoking, neuropathy, and race/ethnicity. Using this model, only neuropathy was a significant independent risk factor for amputation after a burn injury (odds ratio [OR] 18.5 [95% CI 1.8 – 189]).

Discussion

Our previous study of lower-extremity burn injury in patients with diabetes suggested that a relatively small burn injury in such a patient could cause significant morbidity (6). These complications range from burn wound infections to poor wound healing and lower-extremity amputations. In this study, we wanted to examine the patient factors related to diabetes that could increase the risk of amputation of burned lower limbs.

Our current study suggests that a history of diabetic neuropathy independently increases the risk of amputation after a lower-extremity burn injury. This finding correlates with the known pathology and natural history of diabetes.

The lifetime prevalence of neuropathy in patients with diabetes is estimated to be >50%, which correlates with our patient population (56%) (8.9). Neuropathy mostly develops in patients with diabetes who have long-standing hyperglycemia; however, a small proportion of patients newly diagnosed with diabetes (20%) also have neuropathy (10). Most diabetic neuropathy is classified as distal sympathetic neuropathy affecting distal lower limbs in a symmetric stocking net pattern (11). As we noted in our previous study, this stocking net pattern neuropathy results in a numbness and pain for which patients often try to find relief with heat (12,13). The sensory deficit from neuropathy significantly increases the risk of a severe burn injury as patients are unable to feel pain normally (2,14).

The mechanism underlying diabetic neuropathy is not fully understood. It is likely due to increased oxidative stress and direct cellular damage from hyperglycemia (15). Additionally, cellular changes from long-standing hyperglycemia likely underlie factors involved in poor wound healing after injury. A prospective study in patients with diabetes and burn injuries indicates that the time to wound closure is significantly delayed (16). This delay may indirectly be the result of more muscle protein loss with diabetes after a severe burn injury (17). Direct wound healing impairment is likely the result of abnormal neovascularization with diabetes, resulting in a decreased blood supply to burn wounds compared to burn wounds in people without diabetes (18). Microcirculatory abnormalities from vascular endothelial dysfunction, which may decrease leucocyte

migration and nitric oxide synthetase activity, may increase wound infection rates and impair immune-directed wound healing (19). A combination of these factors is likely the underlying cause of increased skin grafting failures in patients with diabetes (20).

We investigated other aspects of diabetes management and glycemic control and found that only A1C differed between burn patients with diabetes who underwent amputation and those who did not require amputation. In our patient population, patients who had an amputation after a burn injury had higher admission A1C levels. However, in our multivariate logistic regression model, A1C was not a significant risk factor for an amputation (OR 1.16 [95% CI 0.9–1.4]). A published study on the diagnostic utility of A1C in burn patients with diabetes indicated that A1C can accurately identify patients with diabetes, but does not affect patient management (21). This study, however, did not analyze specific outcomes such as wound healing and amputation rates. One possibility for our findings is that our study was underpowered to evaluate whether A1C levels are a risk factor for amputation after a burn injury.

Conclusion

In adults with diabetes, lower-extremity burns can result in significant morbidity. Patients with poor glucose control and peripheral neuropathy are more likely to have worse healing of their lower-extremity burn wounds, which increases the likelihood of amputations, the majority of which are amputations of the lower leg. We recommend that lower-extremity burn injuries in patients with diabetes require close follow-up and possible referral to a burn specialist so that interventions and treatment strategies can be implemented to prevent more serious complications such as infection and sepsis. Further studies are needed to determine optimal treatment strategies for these high-risk patients to increase the chances of limb salvage.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

S.S. analyzed the data and wrote the manuscript. A.B. collected the data and edited the manuscript. K.P. and T.P. contributed to the discussion and edited the manuscript. D.G. was involved in the study design, contributed to the discussion, and edited the manuscript. S.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analytics.

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