Association of Inpatient Glucose Measurements With Amputations in Patients Hospitalized With Acute Diabetic Foot

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Context: The association of inpatient glucose measurements with amputations in patients admitted with acute diabetic foot has not been described.

Objective: To evaluate the relationship of hyperglycemia, hypoglycemia, and glucose variability during hospitalization with amputations in patients hospitalized with acute diabetic foot.

Design: Retrospective cohort study.

Setting: Academic tertiary hospital.

Patients: We reviewed demographic, clinical, laboratory, and point-of-care glucose data in patients hospitalized with acute diabetic foot in the Diabetic Foot Unit during 2015 through 2017.

Main Outcome Measures: The primary outcomes were any or major amputations during hospitalization. Secondary outcomes included length of hospitalization and in-hospital mortality.

Results: During the study period, 418 patients were hospitalized in the Diabetic Foot Unit and 45,496 glucose measurements were taken. Patients experiencing any hyperglycemia and any or severe hypoglycemia were more likely to undergo any or major amputations during hospitalization. High glycemic variability was associated with major amputations. Peripheral vascular disease (PVD), high Wagner score, and hypoglycemia were independent predictors of amputations. Older age, PVD, previous amputation, elevated white blood cell level, high Wagner score, and hypoglycemia were independent predictors of major amputations.

Conclusions: In-patient hypoglycemia emerged as an independent risk factor for any and major amputations. Although it is unclear whether hypoglycemia directly contributes to adverse outcomes or is simply a biomarker of disease severity, efforts to minimize in-hospital hypoglycemic events are warranted. (***J Clin Endocrinol Metab*** **104: 5445–5452, 2019)**

Diabetic foot ulcers (DFUs) are a devastating complication of diabetes and have been associated with increased risk of lower-extremity amputation, high morbidity, and mortality (1). The global prevalence of foot ulcers in patients with diabetes is 6.3%, ranging from 3% in Oceania to 13% in North America, with an estimated lifetime incidence as high as 25% (2). It is estimated that 50% to 70% of lower-extremity amputations are preceded by a DFU, and worldwide, a limb is lost due to diabetes every 30 seconds (1). Not only are DFUs a significant

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Abbreviations: CRP, C-reactive protein; CV, coefficient of variation; DFU, diabetic foot ulcer; PVD, peripheral vascular disease; WBC, white blood cell.

financial burden, they result in impairment of quality of life and are associated with reduced life expectancy, with 5-year mortality rates between 43% and 55% (3, 4). Major risk factors for DFUs include sensory loss from advanced peripheral neuropathy, peripheral vascular disease (PVD), diabetes duration, poor glycemic control, smoking, and prior history of DFU or amputation (2, 5).

Extensive evidence from observational and prospective randomized clinical trials demonstrates that both hyperglycemia and hypoglycemia are associated with prolonged hospital stay and poor clinical outcomes, including increased mortality, infections, and in-hospital complications (6). The association correlates with the severity of hyperglycemia on admission as well as during hospitalization. Poor glycemic control has been shown to be associated with increased amputation risk; however, its association with amputations in patients with an established DFU is less clear (7).

The objective of this study was to evaluate the relationship of hyperglycemia, hypoglycemia, and glucose variability during hospitalization for DFU and to examine the association with length of hospital stay, amputation rate and extent, as well as mortality. We hypothesized that tighter glycemic control and lower rates of hypoglycemia would be associated with shorter length of hospitalization and reduced amputation rate.

Materials and Methods

Study setting

This retrospective study was conducted in a Diabetic Foot Unit, located in a large, tertiary hospital. All patients in the unit are managed according to established protocols for glucose monitoring, basal-bolus insulin treatment regimen, and wound treatment in hospitalized patients. Data were collected from electronic medical records in the hospital. For each admission, the clinical condition and medical history of the patient were obtained, including type of diabetes, insulin use, dialysis, ischemic heart disease, smoking, previous amputations, PVD, and previous hospitalizations, as well as regular use of medication. Additionally, the vital signs (temperature and blood pressure) and blood tests [blood glucose, creatinine, white blood cell (WBC) level, C-reactive protein (CRP) level] documented upon admission to the hospital were collected. The Wagner classification score of the ulcer was ascertained by reviewing the text describing the physical examination of the foot. The presence of osteomyelitis (consistent with a Wagner score of 3) was also determined by imaging done on admission.

The study was approved by the hospital's local Helsinki Committee.

Inpatient glucose control

The Diabetic Foot Unit implemented an insulin protocol upon its establishment in late 2010. Per the protocol, all patients are transitioned to basal-bolus insulin therapy upon admission. The starting total daily dose of insulin is 0.3 U/kg, divided equally into a single basal dose and three premeal bolus doses. In the case of premeal sugar exceeding 150 mg/dL, a correction dose of insulin is added to the dose in a stepwise manner. Patients who have already been taking basal insulin prior to admission are prescribed doses similar to their preadmission dosing, with the addition of prandial insulin. Patients on basal-bolus regimens are prescribed their standard regimen with corrections added as needed. Daily glucose measurements and insulin doses administered are reviewed by the treating physician daily and insulin doses are adjusted as needed. An endocrine consultation can be requested *ad hoc*. Additionally, glucose and insulin values are reviewed by a diabetes specialist and diabetes nurse during weekly multidisciplinary rounds.

Inpatient glucose levels are measured using a single departmental glucometer, the Accu-Chek Inform II portable glucometer (Roche Diagnostics), which has advanced connectivity features and automatically records the measured glucose levels in the electronic medical record. The glucometer is calibrated periodically as required by international standards for inpatient care. The Freestyle Optium Neo (Abbott Diabetes Care) is a point-of-care glucometer approved for in-patient use but lacks the connectivity features. It is used in the infrequent event of malfunction of the connected glucometer. It is calibrated periodically as well.

Inclusion and exclusion criteria

All patients admitted between 1 January 2015 until 31 December 2017 with a diagnosis of acute diabetic foot, defined as acute infection of a DFU or acute/critical ischemia in a patient with DFU mandating urgent intervention. Patients were included only when their entire hospitalization was during this period. Admission date was defined as date of admission to the Diabetic Foot Unit, and discharge date was defined as last day in the hospital or mortality. Patients who were hospitalized for ≤ 3 days or had fewer than five glucose measurements were excluded from the study.

Definitions of glycemic variables

Blood glucose values were based on venous blood samples and point-of-care glucose values. Hyperglycemia was defined as at least three blood glucose measurements of $\geq$250 mg/dL (13.9 mmol/L) and severe hyperglycemia as at least three measurements of blood glucose $\geq$350 mg/dL (19.4 mmol/L). These relatively high thresholds were chosen due to the overall poor glycemic control of our multimorbid population, whereby the vast majority exceeded the acceptable inpatient glycemic targets of $<$180 mg/dL (10 mmol/L). Hypoglycemia was defined as at least one blood glucose measurement of $<$70 mg/dL (3.9 mmol/L) and severe hypoglycemia as at least one measurement of blood glucose $<$54 mg/dL (3 mmol/L). Coefficient of variation (CV) was defined as standard deviation of glucose measurements divided by mean blood glucose level. High and low CVs were considered above and below the median accordingly.

Outcomes

The primary outcomes were (i) any amputation during hospitalization or (ii) major amputation, defined as an amputation proximal to the calcaneus. Secondary outcomes included (i) length of hospitalization and (ii) in-hospital mortality.

Statistical analysis

Continuous variables are presented as mean ± SD; categorical variables are presented as number (%). A χ^2 test (for two or more groups) was used to compare the value of categorical variables between all subgroups in this study, and the *t* test was used to compare continuous variables among these subgroups.

The association between covariates and outcomes in multivariate analysis was assessed using logistic regression. We included all variables with $P < 0.15$ in the unadjusted model, which did not have high multicollinearity with other variables in the multivariate analysis. All unadjusted ORs, adjusted ORs, and 95% CIs are presented. Logistic regressions were repeated as a sensitivity analysis, excluding patients with type 1 diabetes.

The statistical analyses for this study were generated using IBM SPSS statistics, version 25.

Results

Study cohort

During the study period, there were 425 admissions. After applying the exclusion criteria, the cohort consisted of 418 hospitalizations. Baseline characteristics are shown in Table 1. Most patients were of male sex, with type 2 diabetes, insulin treated, and with advanced diabetic foot disease. Of note, canagliflozin, which had been associated with increased risk of amputations (8), was not used by any of the patients because it is not approved for use in our country. During this study, 45,496 blood glucose measurements were performed, with a mean of 108.8 measurements per hospitalization and 4.7 measurements per day.

During hospitalization, 305 (73%) patients experienced hyperglycemia, including 124 (30%) with severe hyperglycemia. Hypoglycemia was noted in 201 (48%) patients, including 94 (22%) with severe hypoglycemia. The median glycemic CV was 34%. Baseline characteristics of patients stratified by glucose status are shown in Table 1. Patients who experienced hyperglycemia were more likely to be smokers, using insulin, and with a higher Wagner score. Additionally, they had higher WBC and CRP levels on admission. Patients with hypoglycemia were more likely to be older, on dialysis, have a history of PVD, have higher Wagner score, and receive treatment with insulin. Those with high glucose variability were more likely to be on dialysis and have PVD, an estimated glomerular filtration rate of <60 mL/min/1.73 m^2, insulin use, a higher Wagner score, and elevated baseline WBC and CRP levels.

Outcomes

During hospitalization, 229 (55%) patients had undergone amputation, of whom 108 (47%) had a major amputation. Patients experiencing hyperglycemia or hypoglycemia during admission were more likely to experience any or major amputations. Severe hypoglycemia but not severe hyperglycemia was significantly associated with any and major amputations. High glucose variability was associated with higher risk of major amputations (Fig. 1; Tables 2 and 3). The average length of hospitalization was 23 ± 20.4 days, and the median hospitalization was 17 days (interquartile range, 9 to 31 days). Poor glycemic control was associated with longer length of stay. In-hospital mortality was 6% (26 patients). High glycemic variability was associated with increased mortality ($P = 0.04$), yet the association with hypoglycemia was of borderline significance ($P = 0.07$) (Table 4).

Predictors of amputations

In univariate analyses multiple clinical and laboratory variables were associated with amputations and major amputations (Tables 2 and 3). The multivariate analysis included all significant parameters excluding CRP levels, which showed multicollinearity with WBC levels. Similarly, severe hyperglycemia and hypoglycemia were excluded owing to the inclusion of any hyperglycemia and hypoglycemia, which showed stronger association in the unadjusted model. Increased Wagner ulcer classification score on admission, PVD, and any hypoglycemia were independently associated with any amputations (Table 2). Independent predictors of major amputations included age, WBC level, PVD, a history of previous amputation, Wagner ulcer classification score of 4 to 5 vs 3, and any hypoglycemia (Table 3). Sensitivity analysis excluding patients with type 1 diabetes mellitus showed similar trends, with hypoglycemia remaining an independent predictor of amputations and major amputations.

Discussion

In this retrospective study of hospitalized patients with acute diabetic foot, we demonstrate an independent association of hypoglycemic events and adverse outcomes, including any and major amputations. Although patients who experienced hyperglycemia during hospitalization were more likely to require amputation, it did not emerge as an independent variable.

Previous studies have evaluated the relationship of glycemic control and diabetic foot outcomes. A meta-analysis of nine randomized controlled trials found that intensive glycemic control (HbA1c of 6% to 7.5%) was associated with a 35% reduced risk of amputations in patients with diabetic foot syndrome (1). Other studies have shown mixed results, with some studies showing a direct relationship between HbA1c and wound healing or amputation rate, although most studies were unable to demonstrate an association between acute glycemic control, wound outcome, or amputation rate in patients

Table 1. Baseline Characteristics of Patients by Glycemic Indices During Hospitalization

	Hyper (N = 305)	No Hyper (N = 113)	Severe Hyper (N = 124)	No Severe Hyper (N = 294)	Hypo (N = 201)	No Hypo (N = 217)	Severe Hypo (N = 94)	No Severe Hypo (N = 324)	High CV (N = 209)	Low CV (N = 209)	Overall
Age, y	64.8 ± 12.4	64.7 ± 13.7	64 ± 12.9	65 ± 12.7	66.6 ± 12.7[a]	63.0 ± 12.5	67.5 ± 13.8[b]	63.9 ± 12.3	65.4 ± 12.6	64.1 ± 12.9	64.8 ± 12.8
Male sex	233 (76.4)	78 (69.0)	98 (79.0)	213 (72.4)	146 (72.6)	165 (76.0)	65 (69.1)	246 (75.9)	156 (74.6)	155 (74.2)	311 (74.4)
Type 2 diabetes	282 (92.5)	105 (92.9)	110 (88.7)	277 (94.2)	184 (91.5)	203 (93.5)	81 (86.2)[b]	306 (94.4)	191 (91.4)	195 (93.8)	387 (92.6)
Insulin use	220 (72.1)[c]	53 (46.9)	96 (77.4)[c]	177 (60.2)	143 (71.1)[b]	130 (59.9)	65 (69.1)	208 (64.2)	153 (73.2)[c]	120 (57.4)	273 (65.3)
Current smoking	67 (22.0)[b]	13 (12.4)	32 (25.8)[b]	49 (16.7)	32 (15.9)	49 (22.6)	16 (17.0)	65 (20.1)	41 (19.6)	40 (19.1)	81 (19.4)
IHD	131 (43.0)	43 (38.1)	51 (41.1)	123 (41.8)	89 (44.3)	85 (39.2)	42 (44.7)	132 (40.7)	91 (43.5)	83 (39.7)	174 (41.6)
PVD	208 (68.2)	70 (61.9)	85 (68.5)	193 (65.6)	146 (72.6)[b]	132 (60.8)	68 (72.3)	210 (64.8)	151 (72.2)[b]	127 (60.8)	278 (66.5)
Previous amputation	96 (31.5)	42 (37.2)	48 (38.7)	90 (30.6)	71 (35.3)	67 (30.9)	31 (33.0)	107 (33.0)	70 (33.5)	68 (32.5)	138 (33.0)
eGFR, mL/min/1.73 m^2[d]	67.1 ± 32.2	72.9 ± 33.3	63.0 ± 30.8[b]	71.3 ± 33.1	66.3 ± 29.1	70.6 ± 35.0	61.8 ± 29.7	70.3 ± 33.1	65.1 ± 32.8	71.8 ± 32.1	68.7 ± 32.6
eGFR, <60 mL/min/1.73 m^2	124 (40.7)	36 (31.9)	61 (49.2)[b]	99 (33.7)	74 (36.8)	86 (39.8)	38 (40.4)	122 (37.7)	87 (41.6)[a]	73 (34.9)	160 (38.3)
Dialysis	51 (16.7)	21 (18.6)	15 (12.1)	57 (19.4)	46 (22.9)[a]	26 (12.0)	26 (27.7)[a]	46 (14.2)	47 (22.5)[a]	25 (12.0)	72 (17.2)
WBCs, $10^3/\mu L$	13.6 ± 5.4[b]	11.3 ± 3.9	13.8 ± 5.4[b]	12.6 ± 5	13.3 ± 5.7	12.7 ± 4.6	13.9 ± 10.6	12.7 ± 4.8	13.6 ± 5.7[a]	12.3 ± 4.4	13.0 ± 5.1
CRP level, mg/dL	14.7 ± 11.1[a]	9.5 ± 8.5	17.4 ± 12.1[c]	11.5 ± 9.5	13.1 ± 10.2[c]	13.4 ± 11.1	14.6 ± 11.0	12.9 ± 10.5	14.7 ± 11.5[b]	11.9 ± 9.6	13.3 ± 10.7
Wagner classification											
1–2	21 (6.9)	20 (17.7)	8 (6.5)	33 (11.2)	9 (4.5)	32 (14.7)	5 (5.3)	36 (11.1)	13 (6.2)	28 (13.4)	41 (9.8)
3	104 (34.1)	34 (30.1)	44 (35.5)	94 (32.0)	53 (26.4)	85 (39.2)	27 (28.7)	111 (34.3)	61 (29.2)	77 (36.8)	138 (33.0)
4–5	180 (59.0)	59 (52.2)	72 (58.1)	167 (56.8)	139 (69.2)	100 (46.1)	62 (66.0)	177 (54.6)	135 (64.6)	104 (49.8)	239 (57.2)

Continuous parameters are shown as mean ± SD and categorical parameters as n (%).

Abbreviations: eGFR, estimated glomerular filtration rate; Hyper, hyperglycemia; Hypo, hypoglycemia; IHD, ischemic heart disease.

[a] $P < 0.01$.

[b] $P < 0.05$.

[c] $P < 0.001$.

[d] Calculated by Modification of Diet in Renal Disease, excluding patients on dialysis.

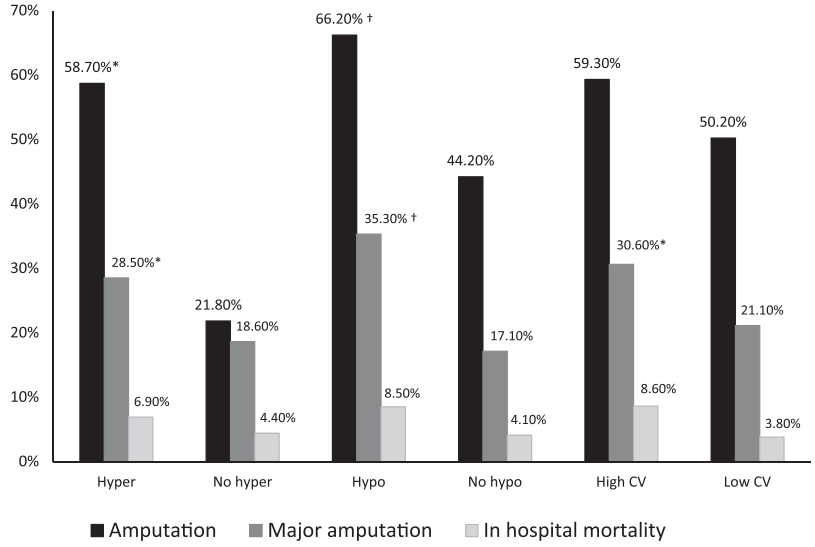

Figure 1. Association of glycemic indices with patient outcomes. $^{*}P < 0.05$, $^{\dagger}P < 0.001$.

with DFUs (2–8). A recent study examined the association between baseline HbA1c and change in HbA1c during treatment with wound healing in patients with DFUs and did not establish a clinically meaningful association between baseline or prospective HbA1C measurements (9). A limitation of the previous data is that glycemic control was determined by HbA1c rather than serial glucose monitoring, which does not capture extent of hyperglycemia, hypoglycemia, or glucose variability.

Our finding of an independent relationship between inpatient hypoglycemia and any or major amputations is of interest. Hypoglycemia is not uncommon in hospitalized patients with diabetes mellitus, with an incidence ranging from 1% to 29%, depending on the definition used for hypoglycemia (10–17). Many factors may contribute to inpatient hypoglycemia, including poor nutrition, diabetes duration, renal failure, heart failure, advance liver disease, advanced age, infection, and intensity of treatment regimen (18–21). Inpatient hypoglycemia is also known to be associated with increased short- and long-term mortality in patients with spontaneous and insulin-related hypoglycemia, as well as longer hospital stay (10, 17, 22). In the current study, we have found an association between inpatient hypoglycemia and any or major amputations. The association between hypoglycemia and mortality was of borderline

Table 2. Predictors Associated With Amputations

	Any Amputation (N = 229)	No Amputation (N = 189)	Unadjusted		Adjusted	
			OR (CI 95%)	*P* Value	OR (CI 95%)	*P* Value
Age, y	66.3 ± 11.7	62.9 ± 13.7	1.02 (1.01, 1.04)	0.0082	1 (0.98, 1.02)	0.89
Male	170 (74.2)	141 (74.6)	0.98 (0.63, 1.53)	0.9318		
Insulin use	156 (68.1)	117 (61.9)	1.32 (0.88, 1.97)	0.1842		
Smoking	48 (21.0)	33 (17.5)	1.25 (0.77, 2.05)	0.3681		
IHD	106 (46.3)	68 (36.0)	1.53 (1.03, 2.28)	0.0337	1.13 (0.68, 1.88)	0.643
Renal function						
eGFR, >60 mL/min/1.73 m^2	95 (41.5)	91 (48.1)	1		1	
eGFR, <60 mL/min/1.73 m^2	86 (37.6)	74 (39.1)	1.11 (0.73, 1.7)	0.6195	0.89 (0.53, 1.49)	0.659
Dialysis	48 (21.0)	24 (12.7)	1.92 (1.09, 3.38)	0.0249	0.8 (0.4, 1.62)	0.5391
PVD	178 (77.7)	100 (52.9)	3.11 (2.04, 4.74)	<0.0001	2.31 (1.36, 3.92)	0.002
Previous amputation	78 (56.5)	151 (53.9)	1.11 (0.74, 1.67)	0.6172	0.94 (0.57, 1.55)	0.8017
Systolic BP, mm Hg	129.7 ± 21.3	133.8 ± 18.7	0.99 (0.98, 1)	0.0411	0.99 (0.98, 1)	0.1941
Diastolic BP, mm Hg	65.2 ± 13.6	69.0 ± 13.65	0.98 (0.97, 0.99)	0.005	1 (0.98, 1.02)	0.9458
WBCs, $10^3/\mu L$	13.5 ± 5.2	12.3 ± 4.9	1.05 (1.01, 1.09)	0.0266	1.02 (0.97, 1.07)	0.4063
CRP level, mg/dL	14.0 ± 11.2	12.4 ± 10.0	1.01 (1, 1.03)	0.1303		
Wagner score 1–2	3 (1.3)	38 (20.1)	0.12 (0.04, 0.42)	0.0008	0.12 (0.03, 0.43)	0.0011
Wagner score 3	54 (23.6)	84 (44.4)	1		1	
Wagner score 4–5	172 (75.1)	67 (35.4)	3.99 (2.56, 6.22)	<0.0001	2.93 (1.77, 4.88)	<0.0001
Hyperglycemia	179 (79.2)	126 (66.7)	1.79 (1.16, 2.77)	0.0088	1.67 (0.93, 2.98)	0.0848
Severe hyperglycemia	74 (32.3)	50 (26.5)	1.33 (0.87, 2.03)	0.1924		
Hypoglycemia	133 (58.1)	68 (36.0)	2.47 (1.66, 3.66)	<0.0001	2.08 (1.24, 3.49)	0.0052
Severe hypoglycemia	66 (28.8)[†]	28 (14.8)	2.33 (1.42, 3.81)	0.0008		
High CV	124 (54.1)	85 (45.0)	1.45 (0.98, 2.13)	0.0623	0.63 (0.36, 1.1)	0.1014

Continuous parameters are shown as mean ± SD and categorical parameters as n (%).

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease.

Table 3. Predictors Associated With Major Amputations

	Major Amputation (N = 108)	No Major Amputation (N = 310)	Unadjusted		Adjusted	
			OR (CI 95%)	*P* Value	OR (CI 95%)	*P* Value
Age, y	70.4 ± 11.1	62.8 ± 12.7	1.05 (1.03, 1.07)	<0.0001	1.04 (1.02, 1.07)	0.002
Male	80 (74.1)	231 (74.5)	0.98 (0.59, 1.61)	0.9276		
Insulin use	79 (73.1)	194 (62.6)	1.63 (1, 2.64)	0.0482	1.56 (0.86, 2.81)	0.1401
Smoking	23 (22.2)	57 (18.4)	1.27 (0.74, 2.17)	0.3859		
IHD	59 (54.6)	115 (37.1)	2.04 (1.31, 3.18)	0.0016	0.94 (0.54, 1.65)	0.8361
Renal function						
eGFR, >60 mL/min/1.73 m^2	34 (31.5)	152 (49.0)	1		1	
eGFR, <60 mL/min/1.73 m^2	42 (38.9)	118 (38.1)	3.58 (1.97, 6.49)	<0.0001	1.8 (0.87, 3.71)	0.1131
Dialysis	32 (29.6)	40 (12.9)	1.59 (0.95, 2.66)	0.0755	1.12 (0.61, 2.08)	0.7132
PVD	98 (90.7)	180 (58.1)	7.08 (3.56, 14.09)	<0.0001	3.16 (1.46, 6.83)	0.0036
Previous amputation	47 (34.1)	61 (21.8)	1.86 (1.18, 2.92)	0.0074	1.98 (1.13, 3.46)	0.0169
Systolic BP, mm Hg	128.2 ± 22.5	132.75 ± 19.3	0.99 (0.98, 1)	0.0446	1 (0.98, 1.01)	0.5472
Diastolic BP, mm Hg	62.9 ± 14.2	68.3 ± 13.3	0.97 (0.96, 0.99)	0.0006	1 (0.98, 1.02)	0.8493
WBCs, $10^3/\mu L$	14.1 ± 5.8	12.6 ± 4.8	1.06 (1.02, 1.1)	0.0076	1.05 (1, 1.11)	0.0351
CRP level, mg/dL	15.1 ± 12.0	12.7 ± 10.8	1.02 (1, 1.04)	0.0478		
Wagner score 1–2	1 (0.9)	40 (12.9)	0.24 (0.03, 1.9)	0.176	0.2 (0.02, 1.67)	0.1353
Wagner score 3	13 (12.0)	125 (40.3)	1		1	
Wagner score 4–5	94 (87.0)	145 (46.8)	6.23 (3.33, 11.67)	<0.0001	3.48 (1.71, 7.12)	0.0006
Hyperglycemia	87 (80.6)	218 (70.3)	1.75 (1.02, 2.99)	0.0408	1.75 (0.87, 3.53)	0.1187
Severe hyperglycemia	36 (33.3)	88 (28.4)	1.26 (0.79, 2.02)	0.333		
Hypoglycemia	71 (65.7)	130 (41.9)	2.66 (1.68, 4.2)	<0.0001	1.98 (1.08, 3.64)	0.0284
Severe hypoglycemia	41 (38.0)	53 (17.1)	2.97 (1.82, 4.84)	<0.0001		
High CV	64 (59.3)	145 (46.8)	1.66 (1.06, 2.58)	0.0261	0.65 (0.34, 1.25)	0.1979

Continuous parameters are shown as mean ± SD and categorical parameters as n (%).

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease.

significance ($P = 0.07$); however, mortality rates were low. Several possible explanations can account for this association. First, hypoglycemia may simply be a marker of more severe illness, and therefore such patients may be more at risk for amputation. As demonstrated by our data, patients who experienced hypoglycemia during hospitalization were more likely to be on dialysis, have PVD, and be on insulin treatment. Second, hypoglycemia may induce a stress response, resulting in endothelial dysfunction and impaired wound healing (23–26). Lastly, acute hypoglycemia has been shown to result in complex vascular effects, including activation of prothrombotic, proinflammatory, and profibrinolytic pathways (27–29). Such changes, especially in the presence of a compromised vasculature, may further contribute to adverse vascular effects or amputation risk.

In our study, review of inpatient glycemic parameters enabled us to analyze the glucose dynamics, including hyperglycemia, hypoglycemia, and glucose variability, during hospitalization. To our knowledge, this is the first study to analyze the relationship between inpatient glucose values and acute diabetic foot outcomes. Although hyperglycemia in our patient cohort was frequent, a significant association with diabetic foot outcomes was not found. The considerable number of hyperglycemic events may be indicative of a sicker patient

Table 4. Association of Glycemic Indices With Length of Stay and Inpatient Mortality

	Length of Hospitalization, Days (Mean ± SD)	*P*	In-Hospital Mortality [n (%)]	*P*
Hyperglycemia	26.4 ± 22.2	<0.001	21 (80.8)	0.35
No hyperglycemia	14.2 ± 10.8		5 (19.2)	
Severe hyperglycemia	31.3 ± 23.3	0.001	9 (34.6)	0.57
No severe hyperglycemia	19.65 ± 18.0		17 (65.4)	
Hypoglycemia	30.7 ± 24.9	<0.001	17 (65.4)	0.07
No hypoglycemia	16.1 ± 11.4		9 (34.6)	
Severe hypoglycemia	34.8 ± 28.2	<0.001	9 (34.6)	0.13
No severe hypoglycemia	19.7 ± 16.1		17 (65.4)	
High CV	26.4 ± 22.1	0.005	18 (69.2)	0.04
Low CV	19.8 ± 18.1		8 (30.8)	

population but may also be attributed to the lack of a computerized insulin-adjustment protocol at our institution. The significance of hypoglycemia but not hyperglycemia in predicting adverse outcomes in patients hospitalized with acute diabetic foot may explain the lack of association of HbA1c with wound healing in some studies. Because HbA1c is a gross measure of glycemic control and may be lower in the presence of hypoglycemic events, the contribution of hyperglycemia to adverse diabetic foot outcomes is not captured when including sick patients with frequent hypoglycemia.

The strength of our study lies in our large cohort of patients admitted with acute diabetic foot, for whom we have computerized access to glucose values and laboratory data throughout the admission. These data have allowed us to analyze the extent of hypoglycemia, hyperglycemia, and glucose variability during hospitalization. Additionally, patients admitted to our Diabetic Foot Unit are treated by a standardized insulin protocol and followed by a multidisciplinary team, which includes a diabetologist and a diabetes nurse.

Several limitations of our study are noted. First, our study is retrospective in nature and the clinical data were extrapolated from the patient files. In particular, the Wagner ulcer classification grade was assessed from the textual description of the physical examination, and not formally documented by the physician at the time of admission. Second, as in any observational study, there may be residual bias or confounders, as patients who were more severely ill were more likely to undergo amputations as well as to experience glucose abnormalities. Third, HbA1c measurements were unavailable, limiting our ability to include glycemic status prior to hospitalization as a factor.

In conclusion, we demonstrate an important association between inpatient hypoglycemia and acute diabetic foot outcomes. Although it is unclear whether hypoglycemia directly contributes to adverse outcomes or is simply a biomarker of disease severity, efforts to minimize in-hospital hypoglycemic events are warranted.

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Additional Information

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Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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