

Diabetic Kidney Disease Is Associated With Increased Complications Following Operative Management of Ankle Fractures

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Abstract

Background: Diabetes mellitus and peripheral neuropathy are established risk factors for complications in operatively treated ankle fractures. Generally, the presence of peripheral neuropathy and diabetic nephropathy have been used as independent variables in studies of diabetic ankle fracture cohorts but are typically treated as binary risk factors. Our purpose was to quantify the effects of risk factors on complication rate specific to diabetic patients undergoing ankle fracture fixation.

Methods: We identified 617 rotational ankle fractures treated operatively at a single academic medical center from 2010 to 2019, of which 160 were identified as diabetic. Of these, 91 ankle fractures in 90 diabetic patients met criteria for retrospective review of clinical and radiographic data. Criteria included perioperative laboratory studies, including glycated hemoglobin (HbA_{1c}) and estimated glomerular filtration rate (eGFR), as well as follow-up radiographs in the electronic record. We defined complications in this surgical cohort as deep surgical site infection, unplanned return to the operating room, and failure of fixation. Logistic regression was performed and odds ratios (ORs) calculated.

Results: The overall complication rate was 28.6% (26/91) in this cohort. Median follow-up was 29 weeks (range: 5–520 weeks). Mean perioperative HbA_{1c} in patients who experienced postoperative complications was 7.6% (range: 5.1%–14.2%) compared with 7.8% (range: 5.6%–13.5%) who did not ($P = .69$). Diabetic patients with chronic kidney disease (eGFR <60 mL/min per body surface area) (OR 5.29, $P = .006$) and peripheral neuropathy (OR 4.61, $P = .003$) were at significantly higher risk of all complications compared with diabetic patients without these comorbidities. Of note, we did not find an association between perioperative HbA_{1c} or body mass index and complication rate.

Conclusion: Patients with diabetes complicated by chronic kidney disease are at significantly higher risk of complications following operative management of ankle fractures. Our study also corroborated previous reports that within this high-risk cohort, the presence of peripheral neuropathy is a significant risk factor for complications. These sequelae of diabetic disease are manifestations of microvascular disease, glycosylation of soft tissues, and impaired metabolic pathways. Identifying these risk factors in diabetic patients allows for patient-specific risk stratification, education, and management decisions of ankle fractures.

Level of Evidence: Level III, retrospective cohort study.

Keywords: ankle fracture, diabetes, chronic kidney disease, peripheral neuropathy, postoperative complications, failure of fixation, surgical site infection

Introduction

Ankle fractures represent 9% of all fractures and are widely known to have an increased risk of complications in diabetic patients.^{9,12,13,19,20,25,26,28,32,34,46,47} An estimated 34.5 million people (10.5%) in the United States are diabetic, a number that is expected to rise to 44.1 million over the next

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decade.^{8,27} Common sequelae of poorly controlled diabetes, most notably peripheral neuropathy, lead to increased risk of surgical site infection (SSI), malunion, nonunion, in-hospital mortality, and amputation.^{19,20,26,28,32,34,46,47} Given the tandem rise of ankle fractures^{4,6,14,29} and diabetes mellitus in the United States, we seek to identify factors that may increase complications in diabetic patients.

Broadly, complications from diabetes mellitus are due to microvascular and macrovascular disease secondary to uncontrolled hyperglycemia.⁴⁵ Peripheral microvascular disease can exist in the absence of macrovascular ischemia, increasing the risk of infection, poor healing, and need for further surgery.^{11,45} Diabetic neuropathy alters protective sensation and gait biomechanics and contributes to ground-level falls and trauma.⁴⁵ Diabetes has been associated with altered reduced osteoblast function,¹⁵ increased cortical porosity, and risk of fragility fractures despite higher average bone mineral density.^{18,37} Additionally, diabetic nephropathy impairs vitamin D metabolism, altering bone healing and likely contributing to the observed increased rate of nonunion in diabetic ankle fractures.⁴⁵⁻⁴⁷

Although operative management of diabetic ankle fractures poses greater risks than nondiabetic ankle fractures,^{33,35} nonoperative treatment of ankle fractures in diabetic patients is associated with a 21-fold increase in complication rates when compared with operative treatment.³⁴ Additionally, those patients undergoing delayed surgical treatment following failed nonoperative management experience up to a 100% complication rate.³⁴ Given these poor outcomes, unstable ankle fractures in diabetic patients are rarely managed nonoperatively.

Although the presence of symmetric, distal peripheral neuropathy and diabetic nephropathy have been used as independent variables in studies of diabetic ankle fracture cohorts, these factors were generally treated as dichotomous in their analysis.^{26,32,38,46} Despite this, the disease severity and diabetic sequelae likely affect complication rates after surgery. Wukich et al's⁴⁶ single-center retrospective cohort study on postoperative complications in diabetic ankle fractures stratified patients based on the presence of complicated diabetes, defined as diabetes-associated peripheral neuropathy, nephropathy, or peripheral arterial disease. Complicated diabetes increased the risk of malunion, nonunion, Charcot arthropathy, and need for revision surgery/arthrodesis when compared to patients with uncomplicated diabetes.⁴⁶ Additionally, Bohl et al⁷ identified end-stage renal disease as a significant risk factor for adverse events including infection and reoperation following ankle open reduction internal fixation (ORIF).

Preoperative workup for diabetic patients commonly includes glycated hemoglobin (HbA_{1c}), metabolic panels, and complete blood counts.¹⁰ HbA_{1c} has become the

standard biomarker for estimating average glycemic levels for the preceding 3 months.²¹ Estimated glomerular filtration rate (eGFR) is calculated based on serum creatinine and patient factors such as age, sex, and weight to calculate kidney function without directly measuring GFR.^{36,39} Chronic kidney disease is diagnosed when eGFR is less than 60 mL/min per body surface area for at least 3 months with evidence of renal injury such as proteinuria.² The prevalence and severity of diabetic neuropathy, kidney disease, and vascular disease is directly correlated with duration of elevated blood glucose.^{3,45} In this study, we seek to quantify and stratify risk of postoperative complications following operative management of diabetic ankle fractures based on perioperative clinical values.

Methods

This was an institutional review board–approved, retrospective review of patient data collected at a single level 1 trauma academic medical center.

Inclusion Criteria

All patients with ankle fractures between January 1, 2010, and December 31, 2019, were identified. All patients aged ≥ 18 years with a diagnosis of diabetes who sustained rotational ankle fractures treated with open reduction and internal fixation by orthopaedic surgery faculty, had electronically reviewable HbA_{1c} (measurement of glycated hemoglobin performed by clinical laboratory), and a comprehensive or basic metabolic panel result recorded within 3 months of the index procedure were included. Patients with at least 1 follow-up appointment were included.

Exclusion Criteria

Patients were excluded if they were <18 years old, sustained a pilon fracture, did not have an index procedure at our institution, did not have laboratory results within 3 months of the index procedure, had absence of a diabetes diagnosis, or postoperative ankle radiographs were unavailable for review.

Data Collection

All medical records were reviewed for relevant information including fracture pattern, whether it was an open injury, age at time of surgery, sex, laterality, smoking status, HbA_{1c}, eGFR, creatinine, end-stage renal disease, peripheral artery disease, body mass index (BMI), insulin dependence status, chronic kidney disease, neuropathy, and chronic obstructive pulmonary disease. Additional data included type of operative treatment (standard ORIF, maximum fixation ORIF, percutaneous

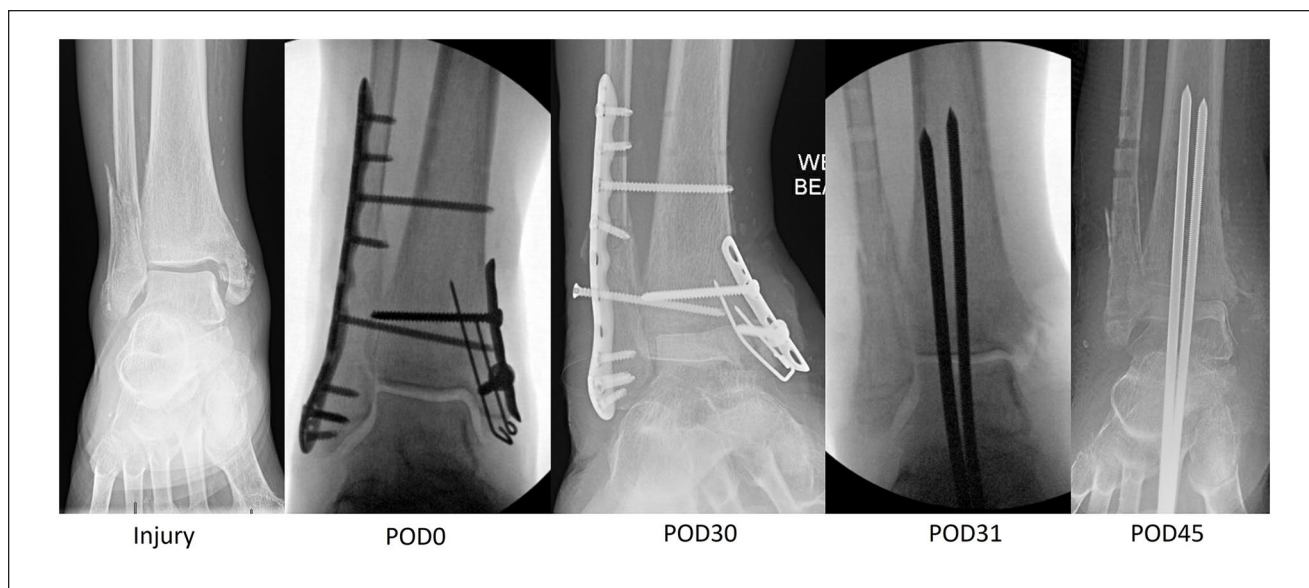


Figure 1. Example radiographs of a patient who underwent maximum fixation open reduction internal fixation and then experienced loss of reduction and deep infection necessitating irrigation and debridement, removal of hardware, and temporary fixation.

fixation, fibular intramedullary nail, external fixator), unplanned return to operating room, unplanned return to surgery in days, revision surgery, days to readmission after discharge, SSI (superficial or deep), failure of fixation (nonunion, malunion), amputation, inpatient days, discharge disposition, and mortality. Maximal fixation ORIF was defined as the use of multiple transsyndesmotom screws and/or rigid locking plate constructs (Figure 1). Race-based eGFR modifiers were not used in our study.^{1,17,24} All radiographs were reviewed to identify failure of fixation constructs or malunion if not captured in the clinical documentation alone.

Radiographic Analysis

Plain radiographs were evaluated by 2 authors using Merge PACS software (2018; IBM Watson Health, Cambridge, MA). All available imaging including postoperative anteroposterior and lateral images of the ankle were reviewed. Anatomic alignment of the tibia was measured on anteroposterior and lateral postoperative radiographs. Failure of fixation was defined based on radiographic criteria outlined by Thordarson et al, which included talar tilt >2 mm, talar subluxation anteriorly or posteriorly >2 mm, eccentric joint space narrowing, asymmetry of the medial or lateral clear space on the mortise view, syndesmotom instability demonstrated by decreased tibiofibular overlap and/or increased tibiofibular clear space and shortening of the fibula assessed with talocrural angles⁴¹ (Figure 1). Radiographic findings were correlated with clinical examination and patient-reported symptoms to clinically define failure of fixation and the decision to return to the operating room.

Sample Size Determination

We identified 617 ankle fractures treated operatively at our institution during the study period. One hundred sixty patients were identified as diabetic; however, 70 were excluded for lacking laboratory studies within 3 months of the index procedure, resulting in a sample size of 91 ankle fractures in 90 patients. A CONSORT diagram depicting the flow of study patients is provided in Figure 2.

Statistical Methods

Descriptive statistics were applied to the variables presented in Table 1. Continuous variables are presented as means with SDs, and binomial variables are presented in proportions. Data were tested for normal distribution using visual inspection of bar charts and Shapiro-Wilk testing. For comparisons of normally distributed continuous variables between 2 cohorts, we used an independent samples Student *t* test. Comparisons of categorical data were performed using χ^2 tests. Comorbidities were analyzed using a univariate logistic regression model to assess association with SSI and complications (coded variable including SSI, unplanned return to operating room, nonunion, malunion). Factors that were found to be significant in the univariate model were then included in a multivariate model. Odds ratios (ORs) were generated using cross-tabulation, and a 2-tailed Fisher exact test was performed to determine statistical significance. All *P* values were 2 tailed. Statistical significance was determined as *P* values $<.05$. All analyses were performed using Stata, version 13.1 (StataCorp, College Station, TX).

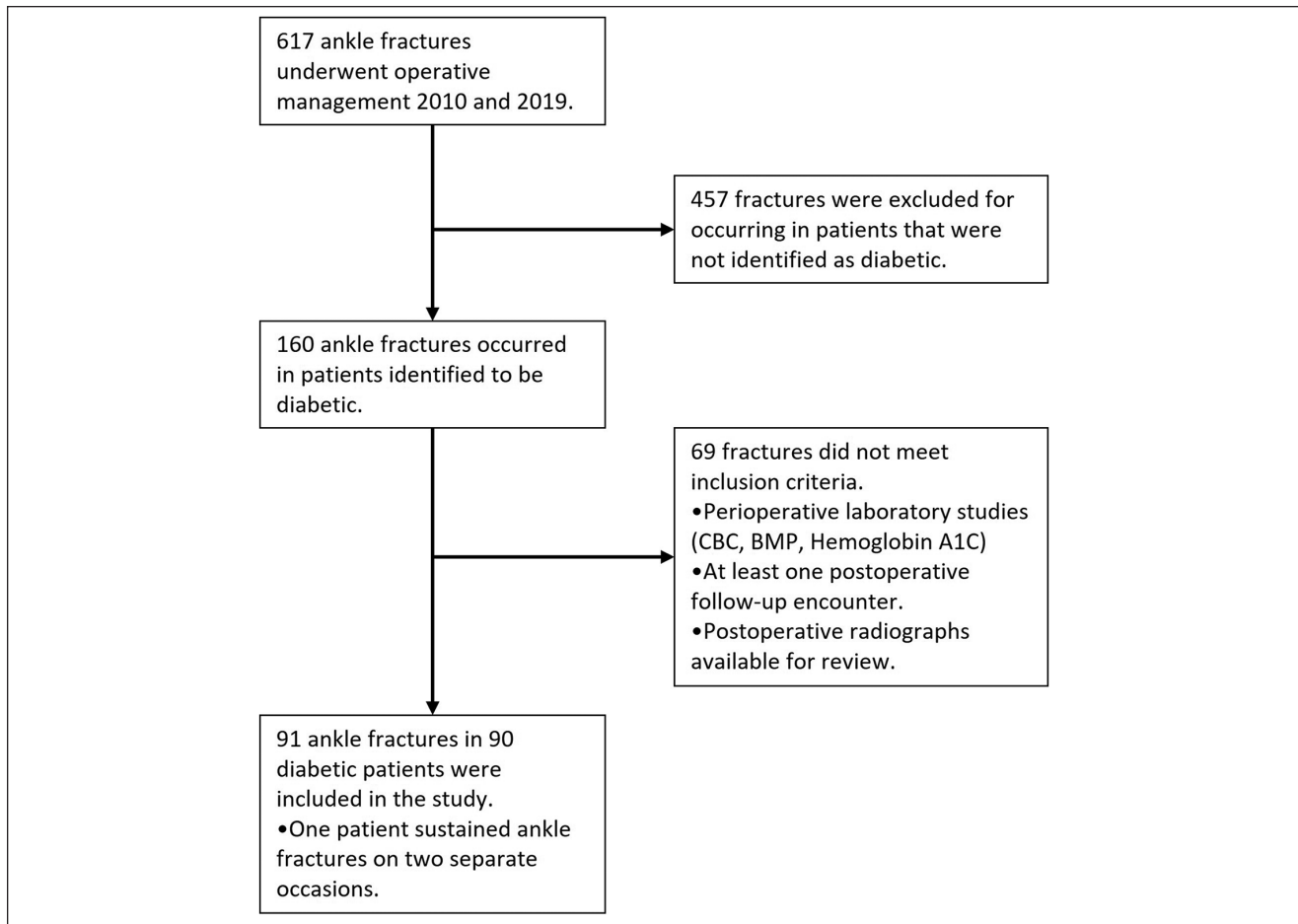


Figure 2. CONSORT diagram depicting flow of patients in the study.

Table 1. Patient Demographics.

Demographics	No Complication (n = 65)	Complication ^a (n = 26)	P Value
Age, y, mean (SD)	59.4 (12.8)	60.9 (14.5)	.63
BMI, mean (SD)	31.7 (7.6)	32.5 (9.2)	.69
Sex, n (%)			
Male	20 (31)	5 (19)	
Female	45 (69)	21 (81)	
HbA _{1c} , %, mean (SD)	7.8 (1.8)	7.6 (2.1)	.69
Insulin dependent, n (%)	32 (49)	16 (62)	.32
Neuropathy, n (%)	18 (28)	15 (58)	.01
Current smoker, n (%)	21 (32)	3 (12)	.04
COPD, n (%)	9 (14)	1 (3.8)	.17
Peripheral arterial disease, n (%)	8 (12)	6 (23)	.19
CKD, n (%)	24 (37)	20 (77)	.001
eGFR, mean (SD)	68.1 (29.5)	43 (31)	.001
Creatinine, mean (SD)	1.4 (1.7)	2.8 (3.7)	.01
ESRD, n (%)	4 (6)	6 (23)	.02

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

P < .05 in Bold.

^aDeep surgical site infection, failure of fixation, unplanned return to operating room.

Table 2. Fracture Characteristics.

	No Complication, (n = 65)	Complication ^a (n = 26)
Fracture pattern, n (%)		
Unimalleolar	8 (12)	1 (4)
Bimalleolar	35 (54)	13 (50)
Trimalleolar	22 (34)	12 (46)
Open fracture	2 (3)	1 (4)
Closed fracture	63 (97)	25 (96)
Type of fixation, n (%)		
Standard ORIF	44 (68)	13 (50)
Maximum fixation ORIF	13 (20)	6 (23)
Percutaneous	2 (4)	2 (7.5)
Fibular IM nail	4 (6)	2 (7.5)
External fixator	1 (2)	3 (12)
Patients with unplanned return to operating room, n (%)	0	15 (58)
Failure of fixation, n (%)	0	
Nonunion, n (%)	0	18 (69)
Malunion, n (%)	0	1 (4)
Return to surgery, d, mean	0	123
Unplanned procedures, n		
Hindfoot fusion	0	6
I&D	0	13
Revision ORIF	0	2
Amputation	0	4
Free flap	0	1
Local flap	0	2

Abbreviations: I&D, irrigation and debridement; IM, intramedullary; ORIF, open reduction internal fixation.

^aDeep surgical site infection, failure of fixation, unplanned return to operating room.

Results

Patient Characteristics

Of the 160 diabetic ankle fracture patients identified (Figure 2), 90 (56%) had an available HbA_{1c} and metabolic panel within 3 months of the index procedure and met inclusion criteria. One patient sustained 2 discrete ipsilateral ankle fractures during the study period and met the laboratory criteria for both injuries. Patient characteristics stratified into “complication” (deep SSI, failure of fixation, unplanned return to operating room) and “no complication” cohorts are detailed in Table 1. There were significantly more patients in the complication cohort with diabetic neuropathy ($P = .01$) and chronic kidney disease ($P = .001$). Mean perioperative HbA_{1c} in patients who experienced postoperative complications was 7.6% (range: 5.1%-14.2%) compared with 7.8% (range: 5.6%-13.5%) who did not ($P = .69$).

Fracture Characteristics and Fixation Techniques

Bimalleolar fractures had the highest prevalence in both cohorts and 3 fractures were open. Standard ORIF was used in 68% of those without complication vs 50% with complication. The complication group had a higher prevalence of maximum

fixation ORIF, percutaneous, intramedullary, and definitive external fixation (Table 2). The overall complication rate was 28.6% (26/91). Fourteen patients required an unplanned return to operating room. The most common unplanned procedures performed were irrigation and debridement, followed by hindfoot fusion. Of the 26 patients included in the complication cohort, 18 (69.2%) were observed to develop a nonunion. Four patients ultimately required amputation (4.4%).

Discharge Disposition

For the complication-free cohort, 60% (39/65) were discharged home compared with 50% (13/26) in the complication cohort. The remainder of patients were discharged to acute or subacute rehabilitation (Table 3). Average inpatient days for the index procedure was longer in the complication cohort (6.7 vs 3.2), and this was statistically significant ($P = .001$). Average orthopaedic follow-up was 60 weeks postoperatively, with a median of 29 weeks and range 5-520 weeks.

Logistic Regression

eGFR ≤ 60 was associated with deep SSI (OR 4.1, 95% CI 1.0-25; $P = .05$) as well as all complications (deep SSI,

Table 3. Discharge Disposition.

Discharge Disposition	No Complication, n (%) or Mean (SD)	Complication, ^a n (%) or Mean (SD)	P Value
Home	39 (60)	13 (50)	
Acute rehab	10 (15)	4 (15)	
Skilled nursing facility	16 (25)	9 (35)	
Inpatient days, d, mean (SD)	3.2 (4.5)	6.7 (5.9)	.001
Duration of orthopaedic follow-up, wk mean (SD)	48.7 (77.4)	89 (93)	
Mortality	7 (11)	2 (8)	
Time to mortality postoperation, wk	181	117	

^aDeep surgical site infection, failure of fixation, unplanned return to operating room.
P < .05 in Bold.

Table 4. Multivariate Analysis of Risk Factors Associated With Complications After Ankle Fracture Surgery in Diabetic Patients.

Risk Factor	Deep SSI		Complication ^a	
	OR (95% CI)	P Value	OR (95% CI)	P Value
eGFR	0.97 (0.94-0.99)	.02	0.97 (0.95-0.99)	.003
Creatinine	1.2 (1.0-1.5)	.04	1.3 (1.0-1.6)	.05
eGFR \leq 90	2.2 (0.26-18.8)	.46	1.6 (0.4-6.2)	.49
eGFR \leq 80	4.8 (0.6-39.5)	.14	3.8 (1-14.2)	.04
eGFR \leq 70	6.2 (0.74-51.2)	.09	5.2 (1.4-19.1)	.01
eGFR \leq 60	4.11 (1.0-25)	.05	5.3 (1.7-16)	.003
eGFR \leq 50	5.5 (1.3-23.3)	.019	4.1 (1.5-11.2)	.006
eGFR \leq 40	8.8 (2.1-37.6)	.003	5.7 (2-16.2)	.001
Peripheral neuropathy	1.89 (0.50-7.1)	.34	4.6 (1.7-12.7)	.003
BMI \geq 30	0.5 (0.14-2)	.36	0.6 (0.2-1.7)	.37
BMI \geq 40	2.1 (0.5-8.9)	.34	1.4 (0.4-4.5)	.58
HbA _{1c} \geq 7%	2.3 (0.6-9.4)	.26	1.1 (0.4-2.9)	.85
HbA _{1c} \geq 8%	1.6 (0.4-6.1)	.51	0.8 (0.3-2.3)	.68
	Superficial SSI		Failure of Fixation	
Peripheral neuropathy	1.5 (0.4-5.5)	.51	8.8 (2.6-30)	.001
eGFR	0.99 (0.9-1)	.81	0.96 (0.9-0.9)	.002
Creatinine	0.98 (0.7-1.3)	.92	1.3 (1-1.7)	.03

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; SSI, surgical site infection.

^aDeep SSI, failure of fixation, unplanned return to operating room.
P < .05 in Bold.

failure of fixation, unplanned return to operating room) (OR 5.3, 95% CI 1.7-16; $P = .003$) (Table 4). Increasing creatinine level was also associated with deep SSI with a lesser effect size (OR 1.2, 95% CI 1.0-1.5; $P = .04$). Unplanned return to operating room (OR 0.97, 95% CI 0.94-0.99; $P = .01$) and failure of fixation (OR 0.96, 95% CI 0.94-0.98; $P = .002$) were inversely associated with GFR. Increasing creatinine level was directly associated with failure of fixation (OR 1.3, 95% CI 1.0-1.6; $P = .02$). Deep SSI was associated with peripheral artery disease (OR 7, 95% CI 1.7-28; $P = .007$). Amputation was associated with superficial SSI (OR 12.4, 95% CI 1.2-126; $P = .03$), deep SSI (OR 34.3, 95% CI 3.1-374; $P = .004$), and

failure of fixation (OR 15.6, 95% CI 1.5-161; $P = .02$). Peripheral neuropathy was associated with total complications (OR 4.6, 95% CI 1.6-12.7; $P = .003$). Of note, HbA_{1c} level and BMI were not associated with the complication, deep or superficial infection, return to operating room, or failure of fixation in our population ($P > .05$).

Discussion

The purpose of this study was to quantify and stratify risk of postoperative complications in diabetic ankle fractures based on commonly obtained perioperative laboratory values and the presence of diabetic sequela. Previous studies have classified

the sequelae of prolonged hyperglycemia through the binary diagnoses of diabetic peripheral neuropathy, vascular disease, and nephropathy.^{9,32,38,46} This study is the first to report that diabetic patients with a perioperative eGFR ≤ 80 mL/min per body surface area demonstrated a significantly higher rate of developing complications (OR 3.8, $P = .04$). The risk further increases for eGFR of 40 mL/min per body surface area or less (OR of 5.7, $P = .003$). Our overall complication rate (28.6%) was similar to rates reported by other retrospective studies (14.2%-34.2%),^{12,46} and peripheral neuropathy was a significant factor for complication in our patients. Lastly, this study did not demonstrate a significant relationship between perioperative HbA_{1c} or BMI and complications. The cohort that did not experience complications had a higher mean perioperative HbA_{1c}; however, the difference was not statistically significant (7.8% vs 7.6%, $P = .69$).

Neuropathy, nephropathy, and retinopathy are manifestations of microvascular tissue damage due to prolonged hyperglycemia.³ Endothelial cells are damaged through direct nonenzymatic glycosylation, increased reactive oxygen species, and multiple dysregulated cellular pathways.³ Following the operative management of ankle fractures, healing is impeded by neuropathic loss of protective sensation and renal osteodystrophy. Additionally, nephropathy and neuropathy are signs of increased bodywide microvascular disease burden, suggesting impaired oxygen and nutrient delivery to the operative site. This slows healing and likely predisposes the patient to infection and nonunion.

The biology of bone healing is altered in patients with diabetes, especially when nephropathy is present. In animal models, hyperglycemia and its resultant tissue alterations has been shown to decrease fracture callus cellularity and tensile strength,⁵ alter bone mineralization and crystalline structure,¹⁶ and decrease soft tissue healing and tensile strength.²² Nephropathy also directly alters bone composition via renal osteodystrophy. The kidneys, in response to parathyroid hormone, directly regulate calcium and phosphate levels and produce 1,25-dihydroxycholecalciferol which regulates intestinal absorption and inhibits parathyroid hormone secretion.⁴⁰ Additionally, the kidneys secrete multiple regulators of bone metabolism and healing, including bone morphogenetic protein 7 and erythropoietin.⁴⁴ In chronic kidney disease, altered mineral handling by the kidney leads to increased secretion of parathyroid hormone, driving demineralization of bone. These factors increase the risk of pathologic fractures, poorer bone quality at the time of surgery, and disruption of minerals and signaling pathways needed for healing. Perioperative eGFR serves as a surrogate for pathologies of bone metabolism in diabetic patients.

Unfortunately, operative management of diabetic ankle fractures cannot be indefinitely delayed so actions may be taken to mitigate risk. Principles from Charcot foot reconstruction including rigid locking constructs and prolonged

immobilization have been adapted to ankle fractures in diabetic patients.²³ In revision cases, arthrodesis serves as a salvage procedure to enable ambulation.^{42,43} Second, strict glycemic control should be maintained in the postoperative setting. Although not demonstrated in our series, other authors have demonstrated increased risk of infection following ankle ORIF for patients with HbA_{1c} greater than 6.5%.³¹ Postoperative hyperglycemia is a demonstrated risk factor for prosthetic joint infections.^{30,48} When appropriate, surgeons should collaborate with internal medicine and/or endocrinology to optimize perioperative glucose control. Additionally, in our study, average length of stay was significantly longer in the complication cohort (6.7 vs 3.2), which warrants further investigation whether prolonged hospitalization is an additional risk factor for poor outcome.

As a retrospective cohort study, this investigation has several limitations. First, because peripheral neuropathy and neuropathy have shared pathogenesis, they are likely not independent variables. Second, our institution does not have a standardized pathway of perioperative management of diabetic ankle fractures, and although many patients were managed by the Foot and Ankle and Trauma subspecialty groups, a large subset of fractures were treated by surgeons of other subspecialties. Thus, perioperative assessment including obtaining laboratory studies, fixation constructs and postoperative protocols were variable among surgeons. This provided a pragmatic approach, although it potentially introduces additional confounders. We excluded patients with incomplete preoperative laboratory workup, which may have introduced selection bias; however, for the study endpoints, this was critical to allow for a comparison between groups. Our assessment of kidney function is at a single time point and did not include other markers for renal dysfunction such as proteinuria. Additionally, although our median follow-up was 29 weeks, some patients were discharged from care 5-8 weeks postoperatively by their surgeon and did not have additional follow-up. Lastly, this study solely focuses on surgical outcomes and did not collect patient-reported outcomes.

Ankle fractures in patients with diabetes mellitus are at risk for potentially devastating complications, putting patients at risk of permanent disability, infection, complex limb salvage operations, and/or amputation. Extended durations of hyperglycemia lead to permanent microvascular damage manifesting as peripheral neuropathy, diabetic nephropathy, and other sequelae. Although acknowledged, it can be difficult to stratify the risk posed by a history of diabetes. Perioperative eGFR is an easily obtained laboratory value that can function as a surrogate indicator of a patient's microvascular disease burden, including underlying neuropathy and altered bone metabolism in the setting of diabetic ankle fractures. This information allows both for the surgeon's acknowledgment of risk as well as education of the patient and family members regarding perioperative risks and expected outcomes. The findings of our

study highlight the importance of treating and preventing diabetic nephropathy. The authors advocate for close primary care follow-up for medical optimization of diabetic patients with ankle fractures. Future studies should investigate medical optimization of diabetic nephropathy in patients with ankle fractures and the effect on postoperative complications.

Ethical Approval

Ethical approval for this study was obtained from University of Chicago Biological Sciences Division Institutional Review Board (IRB20-0431).

Declaration of Conflicting Interests

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