Relationship of Hyperglycemia and Surgical-Site Infection in Orthopaedic Surgery

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Background: The impact of perioperative hyperglycemia in orthopaedic surgery is not well defined. We hypothesized that hyperglycemia is an independent risk factor for thirty-day surgical-site infection in orthopaedic trauma patients without a history of diabetes at hospital admission.

Methods: Patients eighteen years of age or older with isolated orthopaedic injuries requiring acute operative intervention were studied. Patients with diabetes, injuries to other body systems, a history of corticosteroid use, or admission to the intensive care unit were excluded. Blood glucose values were obtained, and hyperglycemia was defined in two ways. First, patients with two or more blood glucose levels of ≥200 mg/dL were identified. Second, the hyperglycemic index, a validated measure of overall glucose control during hospitalization, was calculated for each patient. A hyperglycemic index of ≥1.76 (equivalent to ≥140 mg/dL) was considered to indicate hyperglycemia. The primary outcome was thirty-day surgical-site infection. Multivariable logistic regression models evaluating the effect of the markers of hyperglycemia, after controlling for open fractures, were constructed.

Results: Seven hundred and ninety patients were identified. There were 268 open fractures (33.9%). Twenty-one thirty-day surgical-site infections (2.7%) were recorded. Age, race, comorbidities, injury severity, and blood transfusion were not associated with the primary outcome. Of the 790 patients, 294 (37.2%) had more than one glucose value of ≥200 mg/dL. This factor was associated with thirty-day surgical-site infection, with thirteen (4.4%) of the 294 patients with that indication of hyperglycemia having a surgical-site infection versus eight (1.6%) of the 496 patients without more than one glucose value of ≥200 mg/dL (p = 0.02). One hundred and thirty-four (17.0%) of the 790 patients had a hyperglycemic index of ≥1.76, and this was also associated was thirty-day surgical-site infection (ten [7.5%] of 134 versus eleven [1.7%] of 656; p < 0.001). Multivariable logistic regression models demonstrated that two or more blood glucose levels of ≥200 mg/dL was a risk factor for thirty-day surgical-site infection (odds ratio [OR]: 2.7, 95% confidence interval [CI]: 1.1 to 6.7) after adjustment for open fractures (OR: 3.2, 95% CI: 1.3 to 7.8). A second model demonstrated that a hyperglycemic index of ≥1.76 was an independent risk factor for surgical-site infection (OR: 4.9, 95% CI: 2.0 to 11.8) after controlling for open fractures (OR: 3.3, 95% CI: 1.4 to 8.3).

Conclusions: Hyperglycemia was an independent risk factor for thirty-day surgical-site infection in orthopaedic trauma patients without a history of diabetes.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

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A commentary by Kevin L. Garvin, MD, is linked to the online version of this article at jbjs.org.

The relationship between hyperglycemia and adverse orthopaedic surgical outcomes, such as infectious complications, has been described[1]. Many of these investigations have focused on patients with a history of diabetes mellitus. Uncontrolled diabetes is a significant risk factor for postoperative infection following total joint arthroplasty, spine procedures, and foot and ankle surgery[2-4]. However, nearly one-third of patients who are admitted to the hospital without a history of diabetes have hyperglycemia[5], which is associated with longer hospital stay, higher rates of admission to the intensive care unit (ICU), and increased mortality[6]. Elevated perioperative serum blood glucose levels in general surgery patients increase the risk of postoperative infections, independent of diabetic status[7,8]. While the authors of numerous studies have investigated the effect of hyperglycemia in patients with critical illness[9-12], few have commented on the impact of acute hyperglycemia in patients who are not in the ICU.

The normal physiologic response to injury results in the alteration of endogenous hormone production and metabolites, including increased serum cortisol production, insulin resistance, and subsequent hyperglycemia[13]. Recent investigations suggest that a stress-induced hyperglycemic response following substantial trauma is strongly correlated with clinical outcome, even after consideration of age and injury severity[14-16]. Hyperglycemia was associated with an increased risk of infectious complications in nondiabetic orthopaedic trauma patients[17]. While substantial contributions regarding the topic of perioperative hyperglycemia and outcomes have been made to the general surgery literature, this topic remains largely overlooked in orthopaedic surgery. The purpose of the present study was to evaluate the relationship between hyperglycemia and surgical-site infection in a population of orthopaedic trauma patients without a history of diabetes. We hypothesized that hyperglycemia is a significant independent risk factor for surgical-site infection after controlling for open fractures.

Materials and Methods

Study Design

We performed a retrospective investigation at a university-based level-I trauma center. Following approval by the institutional review board, the institution's Trauma Registry of the American College of Surgeons (TRACS) database was queried for the period of January 1, 2004, through October 1, 2009, to identify patients admitted with isolated orthopaedic injuries requiring acute operative intervention. Baseline demographic information, injury characteristics, and hospital length of stay were obtained from the database (see Appendix). Inclusion criteria were an age of eighteen years or older, isolated orthopaedic injuries requiring acute operative intervention, and an extremity Abbreviated Injury Scale (AIS) score of ≥2. Patients with a history of diabetes mellitus, with an AIS score in any body region other than an extremity, who had received corticosteroids, or had been admitted to the ICU were excluded. Because hemoglobin A1C values were not routinely obtained for every patient during the study period, patients with undiagnosed diabetes mellitus could not be identified in the final population.

Data Collection

All blood glucose values, including both fingerstick and serum levels, were prospectively recorded in the patient's electronic medical record. During the study period, there was no scheduled protocol for blood glucose evaluation in orthopaedic trauma patients who were not admitted to the ICU and had no history of diabetes. Orders for scheduled sliding-scale insulin were not routinely administered. A majority of glucose values were gathered from basic metabolic panel profiles, which included serum blood glucose laboratory values, and were obtained at the discretion of the attending orthopaedic surgeon. Fingerstick glucose measurements were performed by trained nurses using the SureStep Pro Professional Blood Glucose Management System (OneTouch; Lifescan, Milpitas, California). We were unable to determine whether patients had had recent oral intake prior to the laboratory draw; therefore, all glucose values were considered random.

Definition of Hyperglycemia

Hyperglycemia was defined in two ways with use of methods described in the previous literature[5,6,18,19]. First, we defined it as two or more random glucose values of ≥200 mg/dL. Next, we used the hyperglycemic index to describe multiple glucose measurements taken at irregular sampling intervals over a period of time. The index represents the mean glucose level above 108 mg/dL and yields a better estimate of overall glucose control than a single value at admission or the highest value during the day[19,20]. The hyperglycemic index was calculated for each patient in our investigation. To calculate the hyperglycemic index, the area under the curve of all glucose values over the entire hospital stay is plotted. The hyperglycemic index is thus independent of the hospital length of stay. We considered a hyperglycemic index of ≥1.76 (equivalent to ≥140 mg/dL) as a potential marker of hyperglycemia[7,8,18,21]. In order to calculate the hyperglycemic index, patients were required to have at least two measured blood glucose values during the hospital stay. Blood glucose values obtained after the diagnosis of infection (including pneumonia, urinary tract infection, bacteremia, or surgical-site infection) were excluded from analysis to eliminate potential bias—i.e., the possibility that hyperglycemia was a result of the infection rather than a contributing risk factor.

Identification of Surgical-Site Infection

The primary outcome of thirty-day postoperative surgical-site infection was identified with the use of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes for postoperative infection (998.59) and wound dehiscence (998.32). All cases classified as infections were required to have undergone a reoperation for the infection. Superficial infections requiring only oral or topical antibiotics were not considered. The medical records of patients identified via ICD-9-CM codes were reviewed to confirm the presence of either positive intraoperative cultures, pathology specimens with microbiologic pathogens, or visible gross purulence at the operative site within thirty days after discharge from the index trauma admission.

Statistical Analysis

Normally distributed continuous variables were summarized by reporting the mean and standard deviation (SD) and compared by using analysis of variance (ANOVA) testing. Continuous variables that were not normally distributed were presented by reporting the median and interquartile range (IQR) and compared by using the Kruskal-Wallis test. Differences in proportions were compared by using a chi-square test and were reported as a percent frequency. Multivariable logistic regression models were fit to determine the association of the two hyperglycemia markers with the risk of thirty-day surgical-site infection, with adjustment for the potential confounder of an open fracture. Receiver-operator characteristic curves were computed to evaluate the markers of hyperglycemia. All confidence intervals (CI) are at the 95% level, and a two-sided p value of <0.05 indicates significance.

Source of Funding

No external funding was received for the completion of this study.

Results

One thousand eight hundred and eighty-five patients were identified with use of the above listed inclusion criteria.

One thousand six hundred and eighty-one patients had available blood glucose data, and 976 of them met all of the inclusion and exclusion criteria. Seven hundred and ninety patients had two or more blood glucose values, and a total of 4454 glucose values were available for final study analysis. The mean number of glucose values for each patient was 5.6 (range, two to ninety-seven), and on average each patient had at least one blood glucose value obtained daily.

Population demographics and injury characteristics are described in Table I. Orthopaedic injuries included 147 upper-extremity injuries, 144 pelvic or acetabular fractures, 281 femoral fractures, 167 tibial fractures, and fifty-one foot injuries. The most frequent comorbidity was hypertension, and the mean number of comorbidities per patient was 0.5 (SD: 0.7). Three hundred and sixteen patients had a preoperative American Society of Anesthesiologists (ASA) classification of 3 or 4 (indicating severe or life-threatening systemic disease). No patients were identified as ASA class 5 (a moribund patient). In the entire study population, there were twenty-one surgical-site infections, yielding an infection rate of 2.7%. No patient with a surgical-site infection had had a prior infection during the index hospitalization. The mean time to the identification of the surgical-site infection was 20.1 days (range, seven to thirty days). Two hundred and sixty-eight patients (33.9%) had an open fracture, and a surgical-site infection developed in thirteen (4.9%) of them within thirty days (versus eight [1.5%] of the 522 patients with a closed fracture; $p = 0.006$). The rate of infectious complications increased as the type of fracture increased (from Type I to Type II to Type III); however, the difference was not significant ($p = 0.5$). The unadjusted odds ratio for a surgical-site infection following an open fracture was nearly three times greater than that following a closed fracture (OR: 3.3, 95% CI: 1.6 to 10.1). No significant association was noted between the presence of a surgical-site infection and age, number of comorbidities, ASA class, race, tobacco use, Injury Severity Score (ISS), or blood transfusion (Table II).

Evaluation of blood glucose data revealed that 294 (37.2%) of the 790 patients were hyperglycemic on the basis of having two or more glucose values of ≥200 mg/dL. The total number of glucose values was similar between the hyperglycemic and euglycemic patients (5.7, SD: 7.4 versus 5.6, SD: 8.1; $p = 0.9$). Patients with two or more glucose values of ≥200 mg/dL were more likely to be male (214 [43.9%] of 487 men versus eighty [26.4%] of 303 women had two or more glucose values of ≥200 mg/dL; $p < 0.001$). There was no significant association between hyperglycemia and an ASA class of 3 or 4 (118 [37.3%] of the 316 with such an ASA class versus 176 [37.1%] of the remaining 474 had hyperglycemia; $p = 0.95$). Surgical-site infections were more common in patients with two or more glucose values of ≥200 mg/dL (thirteen [4.4%] of 294 versus eight [1.6%] of 496; $p = 0.02$), and the unadjusted risk for thirty-day surgical-site infection was 2.8 (95% CI: 1.2 to 6.9).

One hundred and thirty-four patients (17.0%) were considered hyperglycemic because they had a hyperglycemic index of ≥1.76. There was no significant difference in the number of glucose values obtained between the hyperglycemic and euglycemic patients (6.4, SD: 9.2 versus 5.4, SD: 7.5; $p = 0.2$). Hyperglycemic patients were older than euglycemic patients (51.9, SD: 21.0 years versus 46.9, SD: 21.4 years; $p = 0.01$) and more likely to be male (ninety-eight [20.1%] of 487 men versus thirty-six [11.9%] of 303 women were hyperglycemic; $p = 0.002$). The ISS was similar between the hyperglycemic and euglycemic patients (9.1, SD: 1.7 versus 8.8, SD: 2.2; $p = 0.08$), and there was no association between hyperglycemia and an ASA class of severe or life-threatening (fifty-eight [18.4%] of the 316 with such an ASA class versus seventy-six [16.0%] of the remaining 474 had hyperglycemia; $p = 0.4$). Surgical-site infections were significantly more common in patients with a hyperglycemic index of ≥1.76 (ten [7.5%] of 134 versus eleven [1.7%] of 656; $p < 0.001$), and the unadjusted risk for a surgical-site infection was 4.7 (95% CI: 2.0 to 11.4).

Multivariable logistic regression models were constructed, with adjustment for potential confounding variables, to test the

TABLE I Baseline Demographics and Injury Characteristics

	Total Population (N = 790)
Mean age (SD) *(yr)*	47.7 (21.4)
Male sex *(no. [%])*	487 (61.6)
Race *(no. [%])*	
White	628 (79.5)
Black	125 (15.8)
Hispanic	35 (4.4)
Other	2 (0.3)
Tobacco use *(no. [%])*	111 (14.1)
Comorbidities *(no. [%])*	
Hypertension	239 (30.3)
Coronary artery disease	62 (7.8)
Chronic obstructive pulmonary disease	31 (3.9)
Alcohol abuse	53 (6.7)
Rheumatoid arthritis	9 (1.1)
ASA class *(no. [%])*	
1	51 (6.5)
2	423 (53.5)
3	279 (35.3)
4	37 (4.7)
5	0 (0)
Mean ISS (SD)	8.8 (2.1)
Open fractures *(no. [%])*	268 (33.9)
Type I	19 (7.1)
Type II	103 (38.4)
Type IIIA	103 (38.4)
Type IIIB	25 (9.3)
Type IIIC	19 (7.1)
Blood transfusion *(no. [%])*	291 (36.8)

TABLE II Association Between Variables and Thirty-Day Surgical-Site Infection

	Surgical-Site Infection (N = 21)	No Surgical-Site Infection (N = 769)	P Value
Mean age (SD) *(yr)*	50.8 (15.2)	47.6 (21.6)	0.25
Male sex *(no. [%])*	18 (85.7)	469 (61.0)	0.02
Race *(no. [%])*			0.7
White	16 (76.2)	612 (79.6)	
Non-white	5 (23.8)	157 (20.4)	
Tobacco use *(no. [%])*	2 (9.5)	109 (14.2)	0.55
Mean no. of comorbidities (SD)	0.43 (0.60)	0.50 (0.72)	0.65
ASA class *(no. [%])*			0.56
1	0 (0)	51 (6.6)	
2	12 (57.1)	411 (53.4)	
3	8 (38.1)	271 (35.2)	
4	1 (4.8)	36 (4.7)	
Mean ISS (SD)	8.8 (1.7)	8.8 (2.1)	0.95
Open fractures *(no. [%])*	13 (61.9)	255 (33.2)	0.006
Blood transfusion *(no. [%])*	10 (47.6)	281 (36.5)	0.30
≥2 blood glucose levels ≥200 mg/dL *(no. [%])*	13 (61.9)	281 (36.5)	0.02
Mean no. of total blood glucose values ≥140 mg/L (SD)	1.6 (1.8)	1.5 (3.7)	0.87
Mean total hyperglycemic index (SD)	1.5 (1.2)	0.99 (1.1)	0.03
Hyperglycemic index ≥1.76 *(no. [%])*	10 (47.6)	124 (16.1)	<0.001

association between hyperglycemia and surgical-site infection (Table III). After adjustment for open fractures (OR: 3.2, 95% CI: 1.3 to 7.8), two or more blood glucose values of ≥200 mg/dL remained a significant independent risk factor for thirty-day surgical-site infection (OR: 2.7, 95% CI: 1.1 to 6.7). A second multivariable model was constructed, again with adjustment for open fractures (OR: 3.3, 95% CI: 1.4 to 8.3), and it demonstrated that a hyperglycemic index of ≥1.76 is an independent risk factor for surgical-site infection (OR: 4.9, 95% CI: 2.0 to 11.8). Receiver-operator characteristic curves for the markers of hyperglycemia to predict thirty-day surgical-site infection resulted in an area under the curve of 0.72 and 0.77 for two or more blood glucose values of ≥200 mg/dL and a hyperglycemic index of ≥1.76, respectively (p = 0.29).

TABLE III Results of Multivariable Logistic Regression Analysis of Effect of Hyperglycemia Markers on Thirty-Day Surgical-Site Infection*

	Odds Ratios (95% Confidence Interval)	
	≥2 Blood Glucose Levels ≥200 mg/dL	Hyperglycemic Index ≥1.76
Open fracture	3.2 (1.3 to 7.8)	3.3 (1.4 to 8.3)
Hyperglycemia	2.7 (1.1 to 6.7)	4.9 (2.0 to 11.8)

*The areas under the receiver-operator characteristic curve are 0.72 for the multivariable model with two or more blood glucose values of ≥200 mg/dL and 0.77 for the model with a hyperglycemic index of ≥1.76 (p = 0.29).

Discussion

Hyperglycemia following musculoskeletal injuries is not a new concept to the orthopaedic surgeon. Funsten noted an almost immediate increase in blood glucose levels after injury in a small series of patients without a history of diabetes[22]. The author commented that the small size of the population precluded any definitive conclusions about the matter but further consideration of the issue was necessary. At present, there is a paucity of literature on hyperglycemia in nondiabetic patients following orthopaedic surgery[1]. We therefore performed the present study to evaluate the relationship of hyperglycemia with thirty-day surgical-site infection in a population of orthopaedic trauma patients without a history of diabetes at the time of admission.

Stress-induced hyperglycemia generally refers to an elevation in blood glucose levels during periods of illness[13,23]. While there is no consensus definition, previous authors have noted that, without evidence of prior diabetes, patients with stress-induced hyperglycemia may include those who truly do not have diabetes in addition to those with occult, or previously undiagnosed, diabetes as it not feasible to distinguish between the two at the time of acute physiologic stress[17,23]. Observational studies have shown that more than one-third of patients admitted to the hospital exhibit laboratory signs of hyperglycemia, defined as more than one fasting blood glucose level of ≥126 mg/dL or more than one random blood glucose level of

≥200 mg/dL, with 10% of the population developing newly discovered stress-induced hyperglycemia[6]. This was associated with greater in-hospital mortality, longer hospital stays, and increased rates of admission to the ICU. Additionally, the general trauma and critical care literature is replete with investigations on the relationship of hyperglycemia with morbidity and mortality following critical illness[9-12,15,16], with some authors suggesting that ongoing persistent hyperglycemia and subsequent glucose control are predictive of outcome[21,24]. However, this has not been easily translated into results that may be applied in an environment outside of an ICU.

No patient in our investigation was admitted to the ICU, an important factor that has not been discussed in previous studies on hyperglycemia in surgical patients[7,8,17]. We evaluated a large population of orthopaedic trauma patients who required acute operative intervention and who had no substantial concomitant injuries to other body systems. Results suggest that hyperglycemia is of substantial concern after musculoskeletal trauma. The general surgery literature has demonstrated similar conclusions regarding hyperglycemia and infectious outcomes[7,8]. We used two definitions of hyperglycemia, in accordance with previous literature[5-8] and recent consensus statements by the American Diabetes Association and American Association of Clinical Endocrinologists[18], to determine the potential association with thirty-day surgical-site infection. The risk of infection with either hyperglycemic definition was similar to that associated with an open fracture, which has been described as a significant contributor to posttraumatic infectious complications[25]. While this study cannot confirm that a hyperglycemic index of ≥1.76 is a significantly better predictor of surgical-site infection, compared with two or more random blood glucose levels of ≥200 mg/dL, the results provide further evidence that hyperglycemia following musculoskeletal injury is not a benign phenomenon[8].

There are several important limitations of this study. It was a retrospective investigation, which contains inherent bias. Throughout the study period, there was no standard protocol for routine blood glucose monitoring in patients without a history of diabetes. It is plausible that medically frail patients had more frequent blood glucose monitoring; however, the results demonstrated that there was no difference in the frequency of patients who were hyperglycemic according to ASA class or the number of medical comorbidities. While it is unlikely that nondiabetic orthopaedic patients received sliding-scale insulin orders, the quantification of insulin administration was beyond the capabilities of the present study. Therefore, we cannot make conclusions regarding the optimal management of hyperglycemia in this study cohort. Although we included a large population of fractures, the overall number of thirty-day surgical-site infections was relatively low (n = 21), which limited the number of potential confounding variables that could be included in the multivariable regression analysis. This rate of thirty-day surgical-site infection is similar to those in previous reports on both general surgery and orthopaedic-related operative procedures[3,8]. Additional variables or even yet undefined factors that influence surgical-site infection but were not extrapolated from the data may be further confounding our results. We found that male patients were significantly more likely to have an infection. However, this may be interpreted as a reflection of a trauma population that is predominantly male and likely is not clinically relevant. Difficulty of interpretation and translation of hyperglycemic index values into useful bedside data in routine daily clinical care are also potential drawbacks[26]. Finally, the purpose of our investigation was to evaluate hyperglycemia in orthopaedic trauma patients without a history of diabetes. While authors of previous studies have commented that patients with stress-hyperglycemia may include both undiagnosed diabetics and nondiabetics[17,23], a recent prospective study demonstrated that nearly 5% of general trauma patients were diagnosed with occult diabetes mellitus on the basis of hemoglobin A1C blood values[27]. Such laboratory values were not routinely collected at our institution, and therefore patients with occult diabetes could not be identified from this investigation.

Hyperglycemia is a concern in the posttraumatic and perioperative period and may help to identify a population of patients with musculoskeletal injuries who are at significant risk for infectious complications. As quality health-care measures focus on outcomes-related events, there is presently little discussion about blood glucose monitoring in orthopaedic patients who present without a history of diabetes mellitus[1,28]. While management of blood glucose levels may reach beyond the scope of the general orthopaedic surgeon, this study suggests that recognition of the relationship between hyperglycemia and infectious complications may substantially influence postoperative care of orthopaedic patients. Large prospective, randomized studies are necessary to further delineate the relationship between hyperglycemia and surgical-site infections following orthopaedic surgery.

Appendix

eA A description of the collection of baseline demographic data and injury characteristics and the perioperative antibiotic administration protocol is available with the online version of this article as a data supplement at jbjs.org. ■

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