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# Is postoperative glucose variability associated with adverse outcomes following shoulder arthroplasty?

Allison J. Rao, MD<sup>a</sup>, Nicholas C. Yeatts, BS<sup>a,b</sup>, Risa T. Reid, MD<sup>c</sup>, David P. Trofa, MD<sup>d</sup>, Gregory Scarola, MSPH<sup>e</sup>, Shadley C. Schiffern, MD<sup>a,b</sup>, Nady Hamid, MD<sup>a,b</sup>, Bryan M. Saltzman, MD<sup>a,b,c,\*</sup>

<sup>a</sup>OrthoCarolina Sports Medicine Center, Charlotte, NC, USA

<sup>b</sup>Musculoskeletal Institute, Atrium Health, Charlotte, NC, USA

<sup>c</sup>Department of Orthopaedic Surgery, Atrium Health, Charlotte, NC, USA

<sup>d</sup>Department of Orthopaedics, Columbia University Medical Center, New York, NY, USA

<sup>e</sup>OrthoCarolina Research Institute, Charlotte, NC, USA

**Background:** Postoperative infection after shoulder arthroplasty is a devastating complication. Multiple patient risk factors have been associated with postoperative infection, including increased body mass index and diabetes. Although the association between preoperative glucose control and infection has been established, little is known about the effect of perioperative glycemic control on outcomes following shoulder arthroplasty. The purpose of this study was to investigate the association between postoperative glycemic variability and short-term complications after total shoulder arthroplasty (TSA) and reverse total shoulder arthroplasty (RTSA).

**Methods:** A retrospective study was performed at a large, single-specialty center from January 2015 to December 2018. Patients were included if they underwent primary TSA or RTSA with a minimum of 90 days' follow-up and had a minimum of 1 serum glucose value obtained per day of the hospital stay or had  $\geq$ 3 measurements obtained during the hospital admission period. The primary outcome variable was postoperative infection per accepted definitions of surgical-site infection or periprosthetic joint infection. Secondary outcome variables included stiffness, periprosthetic fracture, periprosthetic dislocation, and reoperation.

**Results:** In total, 1074 TSAs or RTSAs (in 1032 patients) met the eligibility criteria. The mean patient age was  $69.9 \pm 8.4$  years, and 40.3% of patients had a preoperative diagnosis of diabetes mellitus. Of the patients, 670 (62%) had a calculable coefficient of variation. A younger patient age (median, 65 years [interquartile range (IQR), 13.5 years] vs. 71 years [IQR, 11.0 years]; P = .02) and a preoperative diagnosis of diabetes mellitus (P = .01) showed statistically significant associations with postoperative infection. The first in-hospital glucose measurement beyond the reference tertile of 70-140 mg/dL showed a statistically significant association with postoperative infection, with a median of 128.0 mg/dL (IQR, 43 mg/dL) vs. 167.5 mg/dL (IQR, 37.0 mg/dL; P = .01), whereas the second and third glucose measurements showed no association with postoperative infection. We found no associations between the coefficient of variation and reoperations or complications including surgical-site infection, periprosthetic joint infection, death, postoperative infection, periprosthetic fracture, or stiffness.

**Conclusion:** We found an association between a preoperative diagnosis of diabetes mellitus and postoperative infection following shoulder arthroplasty. We also found that an elevated first glucose measurement is associated with the development of postoperative infection. In-hospital glycemic control, as well as preoperative glycemic control and optimization, may be beneficial for reducing post-operative infections following shoulder arthroplasty.

Level of evidence: Level III; Retrospective Cohort Comparison; Treatment Study

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Keywords: Shoulder arthroplasty; infection; diabetes; glucose control; glycemic variability; shoulder infection

This study was approved by the Atrium Health Institutional Review Board (file no. 01-19-20E).

\*Reprint requests: Bryan M. Saltzman, MD, OrthoCarolina Sports Medicine Center, 1915 Randolph Rd, Charlotte, NC 28207, USA. E-mail address: Bryan.Saltzman@orthocarolina.com (B.M. Saltzman).

1058-2746/\$ - see front matter © 2020 Journal of Shoulder and Elbow Surgery Board of Trustees. All rights reserved. https://doi.org/10.1016/j.jse.2020.07.005 Perioperative hyperglycemia after total joint arthroplasty is associated with adverse outcomes, specifically periprosthetic joint infections.<sup>4-6,10,15</sup> This association has been found to be even stronger in patients without diabetes.<sup>9,19</sup> Shohat et al<sup>30</sup> looked more specifically at glucose variability in the postoperative period given its association with increased risks of medical complications, a longer hospital length of stay, and a higher patient mortality rate after non-orthopedic procedures.<sup>17</sup> They found an association with increased rates of surgical-site and periprosthetic joint infections after total joint arthroplasty.<sup>30</sup>

In patients, shoulder arthroplasty has been associated with lower rates of postoperative infection than hip and knee arthroplasty. Glycemic variability and its association with postoperative complications have not been evaluated in shoulder arthroplasty patients. However, the risk of wound complications and deep postoperative infections in patients with diabetes mellitus has been shown to increase as the perioperative hemoglobin  $A_{1c}$  level increases, particularly above 8.0 mg/dL.<sup>3</sup> Thus, the question remains whether glucose variability may similarly provide a useful predictor of the risk of morbidity after shoulder replacement surgery as in the hip and knee literature.

The purpose of this study was to investigate the association between postoperative glycemic variability and shortterm complications following total shoulder arthroplasty (TSA) and reverse total shoulder arthroplasty (RTSA). The results of this study may provide an avenue by which to monitor and reduce patient complications in the early postoperative period after shoulder arthroplasty surgery.

# Materials and methods

This retrospective study was performed at a large, single–orthopedic specialty center with >100 physicians. Using Current Procedural Terminology code 23472 for shoulder arthroplasty (replacement) of both the glenoid and humerus, we queried the records from January 2015 to December 2018.

Independent and potentially confounding variables collected included age, sex, race, ethnicity, body mass index (BMI) at surgery (calculated), Charlson Comorbidity Index (CCI), procedure date, procedure provider, preoperative laboratory values (if available), postoperative glucose measurements including hemoglobin A<sub>1c</sub> level (if available), and date of final follow-up. The inclusion criteria included patients who had undergone primary TSA or RTSA with a minimum of 90 days' follow-up. Patients must have had a minimum of 1 glucose measurement obtained per day or  $\geq 3$  glucose measurements obtained during the hospital stay. The exclusion criteria included patients with extended hospital stays, defined as >30 days, and patients with individual glucose measurements obtained with <5 minutes between measurements showing identical consecutive values.

### Evaluation of glucose measurements

Postoperative blood glucose values were obtained either by bedside measurement of capillary glucose (known as "point-ofcare capillary glucose") or by laboratory-performed analysis (known as "serum glucose"). The first 3 postoperative glucose measurements were recorded if available for each individual's hospitalization. A preoperative diagnosis of diabetes mellitus, as well as any preoperative use of an oral hypoglycemic agent or insulin, was noted. If available, preoperative glucose or hemoglobin  $A_{1c}$  levels were noted.

### Postoperative complications

The primary outcome variable was postoperative infection per accepted definitions of surgical-site infection or periprosthetic joint infection.<sup>21-23</sup> Secondary outcome variables included stiffness, periprosthetic fracture, periprosthetic dislocation, and reoperation. Stiffness was defined as  $<130^{\circ}$  of forward flexion or  $<30^{\circ}$  of external rotation. Any subsequent operation, as well as the reason for reoperation, was noted (ie, irrigation and débridement, resection arthroplasty and placement of antibiotic spacer, or revision arthroplasty) up to final follow-up.

# Statistical analysis

All data underwent descriptive statistical analysis using SAS software (version 9.4; SAS Institute, Cary, NC, USA; http://www.sas.com/software/sas9). Descriptive statistics were produced, and we used the  $\chi^2$  or Fisher exact test for categorical data, the *t* test for continuous normally distributed data, and the Wilcoxon rank sum test for continuous non–normally distributed data. Logistic regression was used to assess the associations of the predictor variables with the coefficient-of-variation tertile for the glucose reading values controlling for the first tertile. The threshold for statistical significance was set at an  $\alpha$  level of .05.

# Results

Among a total of 4419 TSAs or RTSAs, 1074 (in 1032 patients) met the eligibility criteria during the study time frame (Fig. 1). Patient demographic characteristics and glycemic control are presented in Table I. The median follow-up period was 239 days. The mean age was  $69.9 \pm 8.4$  years, and the mean BMI was  $30.9 \pm 6.6$  kg/m<sup>2</sup>. Of the patients, 433 (40.3%) had a preoperative diagnosis of diabetes mellitus. The mean in-hospital glucose level was  $143.1 \pm 39.0 \text{ mg/dL}$ , and the mean coefficient of variation was  $19.1 \pm 13.4$  mg/dL. Table II shows the mean glucose level and standard deviation for each coefficient-of-variation tertile, as well as the percentage of patients with a glucose value outside the range of 70-140 mg/dL. As not all patients had 3 glucose measurements made during hospitalization, only 670 patients (62%) had a calculable coefficient of variation, with 404 eligible patients missing glucose readings, making the coefficient of variation incalculable.

# Demographic and CCI association with postoperative infection

The following variables were entered into a multivariate analysis model: ethnicity, race, sex, age, deceased status,

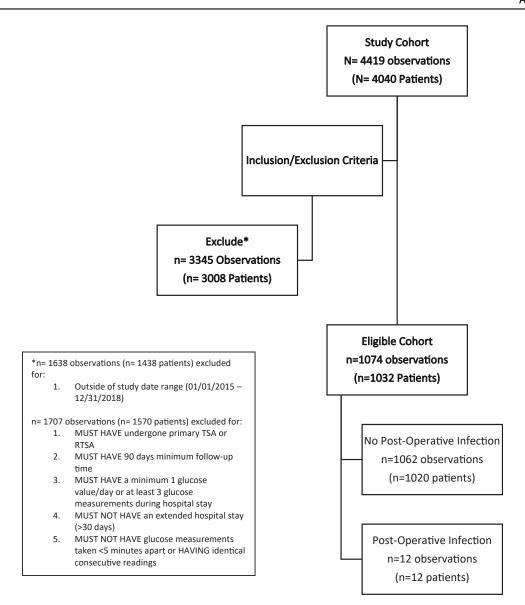


Figure 1 Eligibility diagram. TSA, total shoulder arthroplasty; RTSA, reverse total shoulder arthroplasty.

and BMI (Table III). A younger age (median, 65 years [IQR, 13.5 years] vs. 71 years [IQR, 11.0 years]; P = .02) showed a statistically significant association with post-operative infection. BMI, ethnicity, race, and sex showed no statistically significant associations with postoperative infection.

The CCI takes into account diabetes mellitus, liver disease, solid tumor, acquired immunodeficiency disorder, renal disease, congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease, peripheral vascular disease, cerebrovascular disease, hemiplegia, dementia, connective tissue disease, leukemia, lymphoma, and peptic ulcer disease. Only diabetes mellitus showed a statistically significant association with postoperative infection (P = .01, Table IV).

# Association of glucose variability and diabetes with postoperative infection

Postoperative glucose variability was stratified by the first, second, and third measurements. An elevated first glucose measurement showed a statistically significant association with postoperative infection, with a median of 128.0 mg/dL (IQR, 43 mg/dL) vs. 167.5 mg/dL (IQR, 37.0 mg/dL; P = .01). The second and third glucose measurements showed no association with postoperative infection (Table V). The glucose measurements showed dysglycemia in 42.5% of patients, and 56.6% of the levels of dysglycemia were in patients with diabetes. The relative risk of postoperative infection in patients with dysglycemia among nondiabetic patients was 4.5 (95% confidence interval, 0.4-49.0), which

#### Table I Patient demographic data

	Study population (N = 1074)
Age, median (IQR), yr	70.0 (11.0)
BMI, median (IQR), kg/m <sup>2</sup>	30.1 (8.3)
White race, n (%)	924 (86.0)
Female sex, n (%)	621 (57.8)
Not deceased, n (%)	1058 (98.5)
Diagnosis of type II diabetes, n (%)	433 (40.3)
Patient follow-up, median (IQR), d	239.0 (278.0)
CCI 10-yr survival, median (IQR)	77.5 (56.1)
Postoperative glucose control, median (IQR)	
Glucose level throughout hospitalization, mg/dL	133.0 (44.7)
Coefficient of variation	16.3 (15.0)
IOR interquartile range: BML body mass index: CCL Charlson Comorbidity Index	

*uk,* interqu range; BMI, body mass index; CCI, Charlson Comorbiality Index

Table II         Postoperative	e glucose coef	ficient-of-variation te	rtiles			
Coefficient-of-variation tertile	n* (%)	Median coefficient of variation	Glucose level, mg/dL		g/dL single measurement	
			Median	IQR	outside 70- to 140-mg/dL range	140-mg/dL range
	223 (33.3)	7.273098	124.8	35.8	9.4	37.1
Second (12.22-22.04)	224 (33.4)	16.32398	142.6	45.7	21.4	52.9
Third (≥22.05)	223 (33.3)	29.92734	156.5	62.5	30.5	59.5

*IQR*, interquartile range.

\* Only 670 patients had a calculable coefficient of variation; 404 eligible patients did not have sufficient glucose readings to calculate the coefficient of variation.

	Postoperative inf	fection			
	No (n = 1062)		Yes (n $=$ 12)		P value
Age, yr, Median (IQR)	1062	71 (11.0)	12	65 (13.5)	.02
BMI, kg/m <sup>2</sup> , Median (IQR)	733	30.1 (8.3)	12	31.1 (9.3)	.62
Ethnicity <sup>*</sup> , n (%)					
Hispanic or Latino	12 (1.2)		—		
Not Hispanic or Latino	967 (94.8)		11 (91.7)		
Unknown	41 (4.0)		1 (8.3)		.48
Race <sup>*</sup>					
African American	117 (11.5)		2 (16.7)		
American Indian or Alaskan native	2 (0.2)		—		
Asian	7 (0.7)		—		
White	877 (86.2)		10 (83.3)		
Unknown	15 (1.5)				.73
Sex*					
Female	593 (58.1)		8 (66.7)		
Male	427 (41.9)		4 (33.3)		.77
Deceased <sup>*</sup>					
No	1005 (98.5)		11 (91.7)		
Yes	15 (1.5)		1 (8.3)		.17

IQR, interquartile range; BMI, body mass index.

\* There were 1032 unique patients as these variables will not change at multiple observations.

# Table IV CCI stratified by postoperative infection

	Postoperative infection				
	No (n = 1062)	Yes (n = 12)	P value		
CCI 10-yr survival, median (IQR)	77.48 (56.12)	65.44 (89.02)	.80		
Diabetes mellitus, n (%)					
End-organ damage	54 (7.4)	2 (25.0)			
None	413 (56.3)	1 (12.5)			
Uncomplicated	266 (36.3)	5 (62.5)	.01		
Liver disease, n (%)	· · ·	· · ·			
Mild	17 (2.3)	—			
Moderate to severe	3 (0.4)	—			
None	713 (97.3)	8 (100.0)	>.99		
Solid tumor, n (%)					
Localized	163 (22.2)	2 (25.0)			
Metastatic	4 (0.6)	1 (12.5)			
None	566 (77.2)	5 (62.5)	.05		
AIDS, n (%)	· · ·	· · ·			
No	733 (100.0)	8 (100.0)			
Yes	_ ` ` `	_ /	_		
Renal disease, n (%)					
No	661 (90.2)	6 (75.0)			
Yes	72 (9.8)	2 (25.0)	.19		
Congestive heart failure, n (%)					
No	688 (93.9)	6 (75.0)			
Yes	45 (6.1)	2 (25.0)	.09		
Myocardial infarction, n (%)					
No	692 (94.4)	7 (87.5)			
Yes	41 (5.6)	1 (12.5)	.37		
COPD, n (%)					
No	574 (78.3)	5 (62.5)			
Yes	159 (21.7)	3 (37.5)	.38		
Peripheral vascular disease, n (%)					
Νο	712 (97.1)	7 (87.5)			
Yes	21 (2.9)	1 (12.5)	.22		
Cerebrovascular disease: CVA with mild or no residual or TIA, n (%)					
No	676 (92.2)	8 (100.0)			
Yes	57 (7.8)	_	>.99		
Hemiplegia, n (%)					
No	729 (99.5)	8 (100.0)			
Yes	4 (0.6)		>.99		
Dementia, n (%)	. ()		,		
No	722 (98.5)	8 (100.0)			
Yes	11 (1.5)		>.99		
Connective tissue disease, n (%)	()		,		
No	654 (89.2)	8 (100.0)			
Yes	79 (10.8)		>.99		
Leukemia, n (%)	/3 (10.0)		2.55		
No	726 (99.1)	8 (100.0)			
Yes	7 (1.0)		>.99		
Lymphoma, n (%)	, (1.0)		2.55		
No	728 (99.3)	8 (100.0)			
Yes	5 (0.7)		>.99		
	5 (0.7)		/.55		
Pentic ulcer disease n (%)					
Peptic ulcer disease, n (%) No	702 (95.8)	8 (100.0)			

CCI, Charlson Comorbidity Index; IQR, interquartile range; AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack.

	Postoperative infection						P value
	No			Yes			
	n	Median	IQR	n	Median	IQR	
Glucose value, mg/dL							
DOS	382	128.0	48.0	9	-138.0	56.0	.14
First glucose measurement	1059	128.0	43.0	12	167.5	37.0	.01
Second glucose measurement	602	146.5	61.0	11	170.0	96.0	.16
Third glucose measurement	470	158.0	71.0	9	163.0	65.0	.39
% change							
DOS to first measurement	382	11.9	30.5	9	33.1	63.7	.87
First measurement to second measurement	602	6.7	36.8	11	6.9	33.2	.60
Second measurement to third measurement	470	2.8	35.4	9	-6.6	28.2	.53

Table V	Glucose	variability	stratified	by	postoperative	infection
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IQR, interquartile range; DOS, date of surgery.

was not statistically significant (Table VI). However, diabetes did show a statistically significant association with postoperative infection. A postoperative infection developed in 3 of 636 patients without diabetes compared with 9 of 424 patients with diabetes (P = .02, Table VII).

# Association between glucose variability and complication rate

We found no associations between the coefficient of variation and reoperations or complications including surgicalsite infection, periprosthetic joint infection, death, postoperative infection, periprosthetic fracture, or stiffness (Table VIII).

# Discussion

This study found an association between a preoperative diagnosis of diabetes mellitus and postoperative infection following shoulder arthroplasty. In addition, it found that an elevated first postoperative glucose measurement was associated with the development of postoperative infection. However, it was also shown that dysglycemia in nondiabetic patients was not associated with the risk of postoperative infection, suggesting that diabetes and associated

<b>Table VI</b> Postoperative infection stratified by glucose levelin nondiabetic patients				
Glucose level	Postoperative infection, n (%)		RR (95% CI)	<i>P</i> value
	Yes	No		
Dysglycemia	2 (66.7)	196 (30.8)		
Normal	1 (33.3)	441 (69.2)	4.5 (0.407-48.950)	.228
RR, relative risk; CI, confidence interval.				

in-hospital first glucose measurements may be linked in an association with the risk of postoperative infection. Glucose variability was not found to be associated with reoperation, death, dislocation, periprosthetic fracture, or stiffness.

Although we found that an elevated first postoperative glucose measurement was associated with postoperative infection, the second and third measurements were not found to be associated. This may have occurred because an elevated glucose measurement triggered an intervention such as administration of insulin or an oral hyperglycemic agent. This potentially could have resulted in lower values for the second and third glucose measurements. The first glucose measurement likely represents a patient's baseline glucose level without intervention and may further indicate that preoperative diabetes and poor glycemic control comprise a risk factor for the development of postoperative infection. This is the first study to specifically look at the association of postoperative glucose control with complications following shoulder arthroplasty.

Although we found that preoperative diabetes is associated with postoperative infection, uncertainty still exists on the association between a preoperative diagnosis of diabetes and adverse outcomes in shoulder arthroplasty.<sup>14</sup> Alsubheen et al<sup>1</sup> found in a cohort of 140 patients that diabetes did not affect outcomes, including patient-reported outcomes, strength, and range of motion, following shoulder arthroplasty when compared with nondiabetic patients. Similarly, Jeon and Rhee<sup>11</sup> reported no difference in patient-reported outcomes in diabetic patients vs. nondiabetic patients

Table VII	Diabetes stratified by postoperative infection				
Diabetes	Postoperative infe	Postoperative infection, n (%) P va			
	No (n = 1062)	Yes (n = 12)			
No	637 (60.0)	3 (25.0)			
Yes	425 (40.0)	9 (75.0)	.02		

 Table VIII
 Glucose variability and complications

	n (%)*
Reoperation	
First tertile	13 (1.9)
Second tertile	16 (2.4)
Third tertile	7 (1.0)
Surgical-site infection	
First tertile	—
Second tertile	2 (0.3)
Third tertile	1 (0.1)
Periprosthetic joint infection	
First tertile	1 (0.1)
Second tertile	6 (0.9)
Third tertile	3 (0.4)
Death	
First tertile	2 (0.3)
Second tertile	2 (0.3)
Third tertile	4 (0.6)
Dislocation	
First tertile	4 (0.6)
Second tertile	6 (0.9)
Third tertile	3 (0.4)
Postoperative infection	
First tertile	1 (0.1)
Second tertile	7 (1.0)
Third tertile	3 (0.4)
Periprosthetic fracture	
First tertile	9 (1.3)
Second tertile	10 (1.5)
Third tertile	8 (1.2)
Stiffness	
First tertile	34 (5.1)
Second tertile	42 (6.3)
Third tertile	49 (7.3)

 $^{\star}$  Percentages were calculated from the 670 patients with calculable coefficients of variation.

following shoulder arthroplasty. Diabetes was also not found to be related to active forward elevation or external rotation but did show a statistically significant association with loss of internal rotation.<sup>12</sup> In a study using the National Surgical Improvement Program Ouality database, non-insulin-dependent diabetic patients had risk profiles similar to those of nondiabetic patients after adjustment for demographic characteristics and comorbidity burden.<sup>7</sup> Non-insulin-dependent diabetic patients did not have significantly greater odds of any endpoint including stroke, sepsis, wound complications, blood transfusion, or extended length of stay after shoulder arthroplasty compared with insulin-dependent diabetic patients. Our study similarly found no association between diabetes and postoperative complications of stiffness, periprosthetic fracture, or death. We did, however, find a statistical association between preoperative diabetes and the development of postoperative infection.

In a national database study in patients with diabetes who underwent shoulder arthroplasty, diabetic patients were shown to have significantly higher rates of wound complications and deep infection, both of which increased markedly as the perioperative hemoglobin  $A_{1c}$  level increased.<sup>3</sup> In comparison, Lung et al,<sup>13</sup> McElvany et al,<sup>16</sup> Ponce et al,<sup>24</sup> and Statz et al<sup>32</sup> all found that diabetic patients showed no significantly increased association with infection following shoulder arthroplasty. We did find that a preoperative diagnosis of diabetes was associated with the development of postoperative glucose level had an association with infection. Thus, in our study, there was a relationship between absolute glucose values > 140 mg/dL and the development of postoperative infection.

Similarly to the literature on total knee and total hip arthroplasty, our study found that glucose variability was associated with the development of postoperative infection following shoulder arthroplasty; however, we did not find an association with other adverse outcomes.<sup>8,20,26,29,30,33,34</sup> The rate of periprosthetic infections, both deep and superficial, is currently higher after total knee and total hip arthroplasty than after shoulder arthroplasty. Many factors may be at play, including soft tissue coverage, range of motion, weight bearing, postoperative immobilization, commensal bacteria, and biome.<sup>2,25,27,28,31</sup> However, overall, we did find a similar association in shoulder arthroplasty to that in hip and knee arthroplasty.

Additionally, we found an association between patient age and the development of postoperative infection. Morris et al<sup>18</sup> looked at several risk factors associated with infection after shoulder arthroplasty. They found that smoking, prior rotator cuff repair, prior fracture, rheumatoid arthritis, and patient age  $\leq 65$  years were all statistically significant risk factors for the development of infection. Similarly, we found that patients in whom a postoperative infection developed showed a statistically significant difference in age, with patient age < 65 years showing an association with the development of postoperative infection. Our results confirm that age is a risk factor for the development of postoperative infection after shoulder arthroplasty. This may be because younger patients have increased sebum production in the axilla, which harbors growth of Cutibacterium acnes, a common pathogen in shoulder infection.<sup>25</sup> It is interesting to note that in contrast to prior studies, we did not find that an increased BMI had an association with postoperative infection.<sup>35</sup>

# Limitations

The main limitation of our study is its retrospective design. We were unable to control the timing or number of glucose readings, which may be especially relevant in terms of their timing around meals. Additionally, data on the use of glucocorticoids during the surgical procedure were not available. Furthermore, although diabetic patients were routinely monitored for blood glucose levels with a standard protocol postoperatively, measurement in nondiabetic patients was not standardized. Moreover, although we did exclude patients with a hospital stay > 30 days, length of hospital stay was not evaluated given the variability in the number of hospitals where procedures were performed and external factors such as family support altering lengths of stay, complications during hospital stay, or final discharge disposition. Similarly, for this reason, the total number of glucose measurements, as well as their respective values, was not recorded as this would be affected and not controlled by the length of hospital stay. Finally, as this was a retrospective study requiring review of the medical chart, not all information was recorded as reported in the CCI.

# Conclusion

We found an association between a preoperative diagnosis of diabetes mellitus and postoperative infection following shoulder arthroplasty. We also found that an elevated first glucose measurement is associated with the development of postoperative infection. In-hospital glycemic control, as well as preoperative glycemic control and optimization, may be beneficial for reducing postoperative infections following shoulder arthroplasty.

# Disclaimer

The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

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