Perioperative glycemic control and postoperative complications in patients undergoing emergency general surgery: What is the role of Plasma Hemoglobin A1c?

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BACKGROUND: Plasma hemoglobin A1c (HbA1c) reflects quality of glucose control in diabetic patients. Literature reports that patients undergoing surgery with an elevated HbA1c level are associated with increased postoperative morbidity and mortality. The aim of our study was to evaluate the impact of HbA1c level on outcomes after emergency general surgery (EGS).

METHODS: We performed a 3-year analysis of our prospectively maintained EGS database. Patients who had HbA1c levels measured within 3 months before surgery were included. Patients were divided into two groups (HbA1c < 6 and HbA1c ≥ 6). Our primary outcome measures included in-hospital complications (major and minor complications), hospital and intensive care unit length of stay, and mortality. Secondary outcomes measures were 30-day complications, readmissions, and mortality. Multivariate and linear regressions were performed.

RESULTS: Of the 402 study patients, mean age was 61 ± 12 years, 53% were females, and 63.8% were diabetics. Overall, 49% had an HbA1c ≥ 6%; the mortality rate was 6%. Those with hypertension, history of coronary artery disease, and body mass index of 30 kg/m^2 or greater were more likely to have HbA1c of 6.0% or greater. 7.9% patients experienced major complications. Patients with HbA1c of 6% or greater had a higher complication rate (36% vs 11%, $p < 0.001$) than those with HbA1c less than 6%. However there was no difference in mortality between two groups ($p = 0.09$). After controlling for confounders, HbA1c ≥ 6.0% (odds ratio [OR], 2.9; $p < 0.01$) and a postoperative random blood sugar (RBS) of 200 mg/dL or greater (OR, 2.3; $p < 0.01$) were independent predictors of major complications. Patients with both HbA1c of 6.0% or greater and postoperative RBS of 200 or greater had higher odds (OR, 4.2; $p < 0.01$) of developing major complication. After adjusting for confounders, a higher HbA1c was independently correlated with a higher postoperative RBS (b = 0.494, [19.7–28.4], $p = 0.02$), but there was no correlation with the preoperative RBS.

CONCLUSION: Patients with HbA1c of 6.0% or greater and a postoperative RBS of 200 mg/dL or greater have a four times higher risk of developing major complications after EGS. A preoperative HbA1c can stratify patients prone to develop postoperative hyperglycemia, regardless of their preoperative RBS. (*J Trauma Acute Care Surg.* 2018;84: 112–117. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prognostic, level III.

KEY WORDS: Glycosylated hemoglobin; perioperative glucose control; postoperative complications.

Diabetes mellitus has become a worldwide epidemic and its incidence continues to increase dramatically. According to the World Health Organization, an estimated 347 million worldwide have diabetes.[1] With the changing lifestyle, decreased physical activity, and increasing obesity, the problem is further substantiated and has significant implications in the developed countries. The Centers for Disease Control and Prevention has estimated that there are approximately 29.1 million people with diabetes in the United States, about 9.3% of the total population.[2] Patients with diabetes have doubled health care costs compared to those without diabetes. The total cost of diabetes and prediabetes in the United States is approximately US $322 billion.[3]

Patients with diabetes are more likely to require surgery than the general population. It is estimated that every one in four diabetic patients will undergo surgery at some stage in their life.[4] Moreover, acute illness results in worsening of hyperglycemia because of the increase in circulating stress hormones, especially glucocorticoids and catecholamines.[5,6] Physiologic changes accompanying a surgical procedure can also contribute to the worsening of glycemic control. The resulting hyperglycemia due to an abnormal glucose balance is a risk factor for postoperative complications that include poor wound healing and postoperative infections as well as an increase in morbidity, mortality, intensive care unit (ICU) admission, and hospital length of stay (LOS).[7–9] Evidence suggests that early identification of patients at risk for developing worsening glycemia and careful management of glucose levels in these patients undergoing major surgeries including cardiac and orthopedic; these complications can be reduced if not prevented.[10,11]

The American Diabetes Association recommends lowering the glycosylated hemoglobin (plasma hemoglobin A1c [HbA1c]) to 7% or less in the general population, and recommends a target glucose range of 140 mg/dL to 180 mg/dL in hospitalized patients.[12,13] However, the literature about glycemic control and its impact on outcomes after emergency general surgery (EGS) is scarce. The aim of our study was to identify EGS patients at risk for postoperative hyperglycemia and worse outcomes and to evaluate the correlation between HbA1c levels and preoperative/postoperative glucose levels. We hypothesized that EGS patients with an elevated preoperative HbA1c are at risk of developing postoperative hyperglycemia and poor outcomes.

METHODS

We performed a 3-year analysis (2013–2015) of our prospectively maintained EGS database. The database contains patients managed both operatively and nonoperatively. The institutional review board at the University of Arizona, College of Medicine, approved this study.

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Inclusion and Exclusion Criteria

We analyzed all adult (>18 years) patients admitted to the acute care surgery (ACS) service for which the ACS team was consulted for emergency services and underwent EGS within the indexed admission. All patients who had HbA1c levels measured within 3 months before surgery were included in the analysis. Patients who underwent elective general surgery procedures, those with preoperative sepsis and who died within the first 24 hours of admission were excluded.

Data Points

We reviewed patients who underwent EGS at our Level I trauma/ACS service, and identified those who had their HbA1c levels performed within 3 months before surgery. Each patient's latest HbA1c was used for analysis. Preoperative HbA1c was ordered based on the attending's discretion. We analyzed those who underwent an appendectomy, a cholecystectomy, a hernia repair, or a bowel resection. The following data points were recorded for each patient: patient demographics (including age, sex, and race); vital parameters on presentation, including systolic blood pressure, heart rate, and temperature; laboratory findings, including white blood cell count hematocrit, serum creatinine, erythrocyte sedimentation rate/C-reactive protein levels, and serum albumin; the American Association of Anesthesiologist (ASA) physical status score; and, the hospital and ICU LOS. We also identified the following preoperative comorbidities: congestive heart disease, coronary artery disease, previous stroke and myocardial infarction, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, and malignancy. The preoperative and postoperative blood sugar was extracted from the electronic medical records. The highest postoperative blood sugar within the first 24 hours after surgery was used in all analyses.

Outcome Measures

Our primary outcome measures included in-hospital complications (renal, cardiac, hematologic, neurologic, and infectious), hospital and ICU LOS, and in-hospital mortality. The in-hospital complications were further classified into major and minor complications based on the Clavien-Dindo complication system.[14] Clavien-Dindo III, IV complications were defined as major, while Clavien-Dindo II complications were defined as minor. Secondary outcomes measures were 30-day complications, readmissions, and mortality.

Data Analysis

Data are presented as a mean with standard deviation for continuous parametric data, as a median (with interquartile range) for non-parametric data, and as proportion for categorical variables. We used the Mann-Whitney *U* test and the Student's *t*-test to explore for differences between non-parametric and parametric continuous variables, respectively. Similarly, we used the χ^2 test to identify differences in outcomes between the two groups for categorical variables. For our study, a *p* value less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS (version 20, SPSS, Inc., Chicago, IL).

To assess the association between each potential dependent variable and the binary outcomes, we performed a univariate analysis. Variables with a *p* value less than 0.2 on the univariate analysis were then used in a multivariate logistic regression model. On the multivariate logistic regression analysis, variables were considered significant at a *p* value less than 0.05. The model fit was assessed by the Hosmer-Lemeshow test. In the logistic regression model, the Hosmer-Lemeshow test exceeded 0.05, and the tolerance was greater than 0.1 for all independent variables with a variance inflation factor of less than 10.0.

The receiver operator characteristic curve analysis was performed to determine the cutoff for HbA1c.

RESULTS

A total of 402 patients were included in the analysis. The mean ± SD age was 61 ± 12 years, 53% were females, and 65% were white. The cutoff for the HbA1c was determined to be 6% using the receiver operator characteristic curve analysis for adverse event with a sensitivity and specificity of 85% and 79%, respectively. Overall, 49% of patients had an HbA1c ≥ 6%. The study population was then divided into two groups (HbA1c ≥ 6% vs. HbA1c < 6%). The demographics of the study population are given in Table 1. In terms of age and sex, there was no difference between the two groups. However, compared with patients with a preoperative HbA1c < 6%, those with a preoperative HbA1c of 6% or greater were more likely to be white and have significantly higher body mass indexes and comorbidities (such as hypertension, chronic kidney disease, and a history of stroke/transient ischemic attack).

The outcomes of the two groups are demonstrated in Table 2. Compared with patients with an HbA1c less than 6%, those with a preoperative HbA1c of 6% or greater had higher in-hospital complications (major and minor) and ICU admissions, and they stayed longer in the hospital. However, there was no difference between the ICU LOS and in-hospital mortality between the two groups. On evaluation of 30-day outcomes, patients with an HbA1c of 6% or greater had higher 30-day complication and readmission rates as well. The overall and procedure-specific in-hospital mortality, complications, and 30-day readmission rates are demonstrated in Table 3. The most common surgical procedure is cholecystectomy (28%) followed by appendectomy (27%) and hernia repair (14%).

On multivariate regression analysis, after controlling for confounders including the preoperative blood sugar, an HbA1c of 6.0% or greater (odds ratio [OR], 2.9; 95% confidence interval [CI], 2.5–6.6; $p < 0.01$) and a postoperative random blood sugar (RBS) ≥ 200 mg/dL (OR, 2.3; 95% CI, 1.9–3.7; $p < 0.01$) were independent predictors of major in-hospital complications. However, there was no significant association of either HbA1c (OR, 1.6; 95% CI, 0.8–2.1; $p = 0.21$) or postoperative RBS (OR, 1.3; 95% CI, 0.2–2.8; $p = 0.81$) with in-hospital mortality. Patients with both an HbA1c of 6.0% or greater and a postoperative RBS ≥ 200 had higher odds (OR, 4.2; 95% CI, 2.4–6.7. p < 0.01) of developing major complications, as shown in Table 4. Evaluation of 30-day postdischarge complications and readmissions revealed that patients with an HbA1c of 6% or greater and/or a postoperative RBS of 200 or greater had higher 30-day complications and readmissions. However, none of them was significantly associated with 30-day mortality.

TABLE 1. Demographic and Admission Characteristic of the Two Study Groups

Characteristics	HbA1c ≥ 6% (n = 198)	HBA1c < 6% (n = 204)	*p*
Age: mean ± SD, y	57 ± 7	62 ± 15	0.56
Males	45% (89)	52% (106)	0.16
White	72.1% (143)	60% (122)	*0.01*
Admission vitals			
Fever (TEMP >100.4)	45% (89)	55% (112)	0.05
Tachycardia (HR >100)	58% (115)	52% (106)	0.23
Hypotension (SBP <100)	38% (75)	35% (71)	*0.53*
Admission Laboratories			
Albumin g/dl			
≥ 3.5	70% (139)	82% (167)	0.005
< 3.5	30% (59)	18% (37)	
WBC cells/mm			
≥ 10,000	60% (119)	72% (147)	0.02
< 10,000	40% (79)	28% (57)	
Creatinine, mean ± SD	1.0 ± 0.4	0.7 ± 0.2	0.07
Elevated ESR/CRP	58% (115)	54% (110)	0.63
ASA Class			
> 3	28.5% (57)	22% (40)	0.03
≤ 3	72.5% (141)	88% (160)	
Comorbidities			
CHF	18% (36)	14% (29)	0.34
CKD	21% (41)	10% (20)	<0.01
CLD	11% (22)	12% (24)	0.87
COPD	21% (42)	18% (36)	0.37
HTN	38% (75)	25% (51)	<0.01
Stroke/TIA	13% (26)	7% (14)	0.04
BMI ≥ 30	35% (18)	24% (12)	0.01

HR, heart rate; SBP, systolic blood pressure; WBC, white blood cells; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CHF, chronic heart failure; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; HTN, hypertension; TIA, transient ischemic attack; BMI, body mass index.

TABLE 2. Outcomes

Characteristics	HbA1c ≥ 6% (n = 198)	HBA1c < 6% (n = 204)	*p*
In-hospital outcomes			
Complications			
Major complications	12% (24)	4% (8)	<0.01
Minor complications	24% (48)	7% (14)	<0.01
Renal	25	6	<0.01
Cardiac	12	2	<0.01
Hematologic	6	4	0.53
Neurologic	9	6	0.44
Postoperative infections	20	4	<0.01
Sepsis	5	1	
UTI	4	1	
SSI	9	2	
Wound disruption	2	0	
Hospital LOS	4 [2–6]	2 [2–3]	0.03
ICU admission	18%	9%	0.01
ICU LOS	1 [1–3]	1 [1–2]	0.51
Mortality	8% (16)	4% (8)	0.09
30-d Outcomes			
Complications	16% (32)	6% (12)	<0.01
Readmissions	8% (16)	3.2% (6)	0.02
Mortality	3% (6)	2% (4)	0.53

UTI, urinary tract infection; SSI, superficial surgical site infections.

In addition, logistic regression was performed to identify the correlation between preoperative and postoperative RBS with HbA1c. After adjusting for confounders, a higher HbA1c was independently correlated with a higher postoperative RBS (b = 0.494, [19.7–28.4], $p = 0.02$). However, there was no correlation with preoperative RBS (b = −0.04, [−0.03–0.41], $p = 0.65$).

The adjusted odds of developing a postoperative infection based on preoperative HbA1c levels are demonstrated in Figure 1. HbA1c levels 6% or above result in a linear increase in postoperative infections.

DISCUSSION

Our results suggest that preoperative HbA1c can guide risk stratification and prognostication after EGS irrespective of preoperative glucose levels and diabetes. We performed robust statistical analysis controlling for the possible confounders including the age, sex, race, comorbidities, and the ASA score as well as for diabetes and preoperative glucose levels. We provide evidence that preoperative HbA1c independently predicts postoperative hyperglycemia, and that both are independently associated with increased in-hospital complications, irrespective of the preoperative blood sugar level or the patient's diabetes status. Patients who had both an HbA1c of 6% or greater and an RBS of 200 or greater had a four times higher risk of developing major complications after an EGS. In addition, patients with an HbA1c of 6% or greater also had increased 30-day complications and readmissions. Our study is the first to demonstrate

TABLE 3. Overall and Procedure-specific in-hospital Mortality, Complications, and 30-d Readmission Rates

Procedures	%, (Number)	Mortality	Complications	30-d Readmissions
All EGS procedures	402	6% (24)	23% (94)	5.4% (22)
Cholecystectomy	28% (113)	12% (3)	16% (15)	14% (3)
HbA1c ≥ 6%	16% (64)	8% (2)	13% (12)	9% (2)
HBA1c < 6%	12% (49)	4% (1)	3% (3)	5% (1)
Appendectomy	27% (107)	4% (1)	12% (11)	5% (1)
HbA1c ≥ 6%	12% (48)	4% (1)	10% (9)	5% (1)
HBA1c < 6%	15% (59)	0% (0)	2% (2)	0% (0)
Hernia repair	14% (56)	16% (4)	23% (22)	27% (6)
HbA1c ≥ 6%	9% (35)	12% (3)	18% (17)	18% (4)
HBA1c < 6%	5% (21)	4% (1)	5% (5)	9% (2)
Surgery for bowel obstruction	8% (28)	25% (6)	18% (17)	27% (6)
HbA1c ≥ 6%	4% (14)	16% (4)	13% (13)	18% (4)
HBA1c < 6%	4% (14)	9% (2)	5% (4)	9% (2)
Others	24% (98)	41% (10)	31% (29)	36% (8)
HbA1c ≥ 6%	9% (37)	25% (6)	22% (21)	23% (5)
HBA1c < 6%	15% (61)	16% (4)	9% (8)	13% (3)

TABLE 4. Multivariate Regression Analysis for Outcomes

Characteristics	OR	95% CI	*p*
In-hospital outcomes			
Major complications			
HbA1c ≥ 6%	2.9	2.5–6.6	<0.01
Postoperative RBS ≥ 200	2.3	1.9–3.7	<0.01
HbA1c ≥ 6% + postoperative RBS ≥ 200	4.2	2.4–6.7	<0.01
Minor complications			
HbA1c ≥ 6%	2.2	1.6–3.5	<0.01
Postoperative RBS ≥ 200	4.1	2.4–5.6	<0.01
HbA1c ≥ 6% + postoperative RBS ≥ 200	5.4	4.5–7.5	<0.01
Postoperative infections			
HbA1c ≥ 6%	3.4	2.8–5.1	<0.01
Postoperative RBS ≥ 200	4.1	3.5–6.3	<0.01
HbA1c ≥ 6% + postoperative RBS ≥ 200	8.1	7.5–9.9	<0.01
Mortality			
HbA1c ≥ 6%	1.6	0.8–2.1	0.45
Postoperative RBS ≥ 200	1.3	0.3–2.8	0.81
HbA1c ≥ 6% + postoperative RBS ≥ 200	1.5	0.8–1.9	0.21
HBA1c > 7.5%	1.4	1.2–2.1	0.02
30-d Outcomes			
Readmissions			
HbA1c ≥ 6%	2.1	1.4–4.5	0.01
Postoperative RBS ≥ 200	1.4	1.2–2.6	0.03
HbA1c ≥ 6% + postoperative RBS ≥ 200	2.5	1.7–3.7	0.01
Complications			
HbA1c ≥ 6%	1.7	1.2–2.3	0.02
Postoperative RBS ≥ 200	1.5	1.4–3.1	0.03
HbA1c ≥ 6% + postoperative RBS ≥ 200	3.1	2.1–3.5	0.01
Mortality			
HbA1c ≥ 6%	1.6	0.5–3.4	0.56
Postoperative RBS ≥ 200	1.2	0.2–4.6	0.62
HbA1c ≥ 6% + postoperative RBS ≥ 200	1.1	0.3–3.1	0.45

that an HbA1c of 6% or greater and an RBS of 120 or greater are associated with worse outcomes, whether or not the patient has diabetes.

Glycemic control in hospitalized patients has evolved in the last two decades. The target blood glucose used to be 80 to 110 mg/dL, in keeping with the recommendations of a study of critically ill ICU patients that reported a relative risk reduction of 42% when the glucose levels were maintained below 110 mg/dL.[7] However, a recent meta-analysis of over 26 studies, including the largest, Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation, demonstrated that tightly controlled glucose compared to moderately controlled glucose is associated with increased rates of severe hypoglycemic episodes and increased mortality.[15] This evidence has led to a paradigm shift, and a new glucose target of 140 mg/dL to 80 mg/dL is recommended for most critically ill patients.[16]

Patients undergoing EGS are at a particular risk for complications of hyperglycemia and diabetes because of the urgent nature of the case and the inability to optimize patients before surgery. However, early identification of patients at risk for postoperative hyperglycemia and increased complications may lead to timely intervention to optimize the blood sugars, which may translate to improved outcomes. Our study suggests that patients with an HbA1c of 6% or greater are at a higher risk for postoperative hyperglycemia and the development of complications, and the combined risk is additive, irrespective of diabetes status and preoperative glucose levels. In addition, patients with an HbA1c of 6% or greater had a higher hospital LOS and higher 30-day complications and readmissions. Other studies have reported similar results. Ramos et al.[17] showed that postoperative hyperglycemia increases the risk of postoperative infections and hospital LOS. However, their patient population was heterogeneous and comprised of elective and EGS as well as vascular surgery cases. In another study, the authors found that diabetic patients with high preoperative HbA1c levels were at high risk for surgical site infections after spine surgery.[18] A prospective, single-center, observational cohort study also reported that postoperative glycemic variability and high mean glucose levels averaged over the first 4 postoperative hours is associated with major adverse events after cardiac surgery.[19]

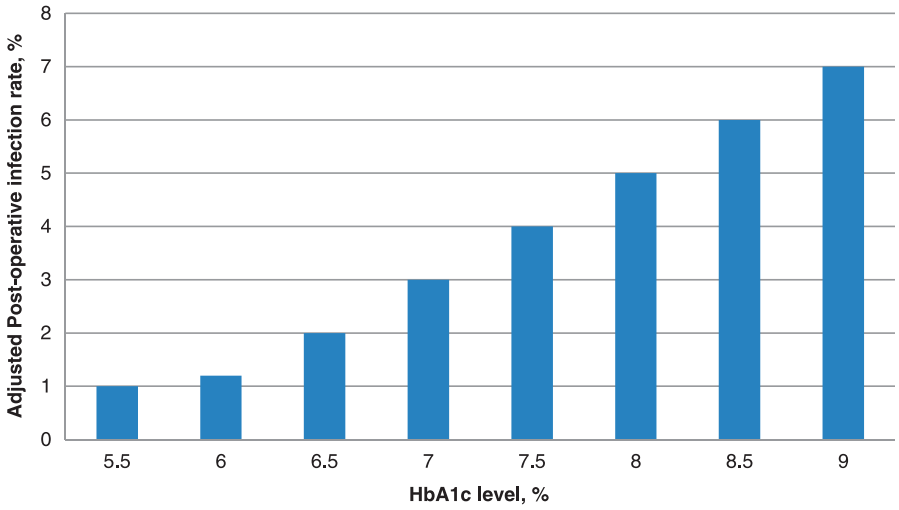

Figure 1. Preoperative HbA1c level and adjusted postoperative infection rate.

We also separately analyzed the adjusted rates of postoperative infections. Patients with an HbA1c of 6% or greater and an RBS of 200 or greater had an 8.1 times higher odds of developing postoperative infections after adjustment for diabetes and other known predictors of postoperative infections. Similar results have been shown in other studies in colorectal surgery patients,[20] orthopedic surgery patients,[21] and gastric bypass[22] and other patient population.

A number of studies have shown that high levels of HbA1c also correlate with mortality after surgery. For instance, Alserius et al.[23] demonstrated that an HbA1c of 6% or greater was associated with increased mortality after coronary artery bypass grafting. However, this was not the case in our study. Our results showed no difference in adjusted mortality rate, even within patients who had both a preoperative HbA1c of 6% or greater and a postoperative RBS ≥ 200. A possible explanation for this might be that an emergency general procedure may be a lower-risk procedure than one in which a patient has either a triple-vessel disease or a two-vessel disease with diabetes that requires coronary artery bypass grafting. Interestingly, when we increased the HBA1c to 7.5% or above in the regression model, we found that patients with an HBA1c of 7.5% or greater had a 40% higher odds of mortality.

Our study has certain limitations. It is retrospective, single-center data that may lack generalizability. In addition, we extracted 30-day outcomes from the medical records, but may have missed patients who presented to some other hospital. Nonetheless, our study reports novel findings of significant association of preoperative HBA1c and postoperative RBS levels with in-hospital and 30-days outcomes, even after adjustment for diabetes and other confound variables.

CONCLUSION

Preoperative measurement of HbA1c may identify patients at a higher risk of poor glycemic control and postoperative complications. Patients with an HbA1c ≥ 6.0% and a postoperative RBS ≥ 200 mg/dl have a 4 times higher risk of developing major complications after EGS independent of the preoperative blood glucose.

AUTHORSHIP

F.J., B.J., M.K., and T.K. designed this study. F.J., B.J., J.S., N.K., M.K., and A.C. searched the literature. F.J., B.J., A.J., M.K., and M.K. collected the data. F.J., B.J., E.Z., and T.K. analyzed the data. All authors participated in data interpretation and manuscript preparation.

DISCLOSURE

The authors declare no conflicts of interest.
The authors have no financial or proprietary interest in the subject matter or materials discussed in the article.

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