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Association between acute phase perioperative glucose parameters and postoperative outcomes in diabetic and non-diabetic patients undergoing non-cardiac surgery

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ABSTRACT

Background: The relationship between acute phase perioperative hyperglycemia and postoperative outcome is poorly understood.
Methods: Retrospective cohort study of diabetic and non-diabetic adult patients undergoing non-cardiac surgery. Mean glucose and glycemic variability during the intraoperative and immediate postoperative periods were compared to length of stay, 30-day mortality, and postoperative complications.
Results: .
Diabetic patients (N = 1096): Higher glycemic variability was associated with longer hospital length of stay (0.32 day per 10 mg/dL) and greater 30-day mortality risk (OR = 1.42). Higher mean glucose (OR = 1.07) and glycemic variability (OR = 1.11) were associated with higher risk of complications.
Non-diabetic patients (N = 1012): Both higher mean glucose (0.29 day per 10 mg/dL) and higher glycemic variability (0.68 day per 10 mg/dL) were associated with longer hospital length of stay. Both higher mean glucose (OR = 1.13) and higher glycemic variability (OR = 1.21) were associated with greater risks of complications.
Conclusions: Poor acute phase perioperative glycemic control is associated with poor outcome, but differently in diabetic and non-diabetic patients suggesting different glycemic management strategies for the two patient groups.

Introduction

Stress induced hyperglycemia is commonly encountered in patients undergoing surgery in both diabetic and non-diabetic patients.[1–3] Though previous studies have shown that uncontrolled hyperglycemia during the perioperative period is associated with poor outcomes,[4–11] a clear differential understanding of the relationship between perioperative glucose levels and postoperative outcome in diabetic and non-diabetic patients is currently lacking. Recommendations by organizations such as the American Diabetes Association (ADA)[12] on perioperative glycemic management are broad and do not specify whether treatment strategies for diabetic and non-diabetic patients should be the same or different. So also, current guidelines do not specify whether intraoperative and immediate postoperative periods when the surgical stress is the highest, requires a different treatment strategy for hyperglycemia. These factors have led to variable approaches to treatment of perioperative hyperglycemia with different glycemic target levels and algorithms adopted in different institutions.[13,14]

Initial studies on perioperative hyperglycemia focused on diabetic patients undergoing cardiac surgery and found a positive association between hyperglycemia and poor outcomes.[4,7,15–17] Later, a similar association was observed in non-cardiac surgery patients, particularly in neuro,[18] colorectal[19,20] and orthopedic[21,22] surgeries. Investigations have mainly focused on diabetic patients because of their compromised pathophysiology of glucose control[15,19,21] with only a few recent studies on non-diabetic patients, that too only in cardiac surgery.[9,23,24] Also, previous studies have

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primarily focused on glucose levels in the postoperative period, particularly in the intensive care units (ICUs).[25–27] The only studies that have explored intraoperative glucose levels have been limited to cardiac[7,16,17] and neurosurgeries.[18] Poor glycemic management could result in not only perioperative hyperglycemia but also high variability in glycemic levels. In cardiac surgery patients in addition to hyperglycemia, high glycemic variability has been associated with poor outcome.[28–30] However, the effect of glycemic variability on patient outcome after non-cardiac surgery remains unclear.

In this retrospective cohort study we explored the association between perioperative glucose parameters during the acute phase and corresponding outcomes after non-cardiac surgery. The acute phase perioperative period for this study was defined as the intraoperative phase and the first 24 h after surgery. We explored the differential effects of mean glucose levels and glycemic variability on postoperative outcomes. Additionally, we explored whether the associations between glucose parameters and outcomes are different in diabetic and non-diabetic patients.

Methods

Institutional approval

This study was approved by the University of Washington Institutional Review Board (IRB) (#38727). The requirement for written informed consent was waived by the IRB.

Study hypothesis

We hypothesized that perioperative mean glucose and glycemic variability are associated with outcomes in patients undergoing non-cardiac surgery. We also hypothesized that the associations are different in diabetic and non-diabetic patients.

Study setting

We performed a single center retrospective cohort study of non-cardiac surgery patients. Our institution is an academic medical center that performs approximately 18,000 adult surgical procedures annually. Our institution follows a perioperative glycemic management protocol that targets a glucose level <140 mg/dL. The protocol is used to manage blood glucose intraoperatively and postoperatively in both diabetic and non-diabetic patients. Both blood glucose measurements made by point of care hospital grade glucose meters and laboratory measurements are used by the protocol. The details of the protocol are described elsewhere.[31,32]

Inclusion and exclusion criteria

This study included non-emergent surgeries other than cardiac procedures with cardiopulmonary bypass (Anesthesia CPTs: 00561-00567) in which the patient underwent general anesthesia. Additionally, procedures with significantly different mechanisms of surgical stress response such as neurosurgery (Anesthesia CPTs: 210-220, 600-670), transplants (Anesthesia CPTs: 00580, 00794, 00796) and obstetric surgery (Anesthesia CPTs: 01958-01969) were also excluded. Both diabetic and non-diabetic patients were included. A patient was considered diabetic if any of the three following conditions were met: 1) pre-anesthesia assessment documentation specifically classified the patient as diabetic, 2) patient had a hemoglobin A1C $\geq$ 6.5 within one year prior to surgery or 3) patient was on insulin or oral hyperglycemic agents. All adult patients ($\geq$18 years) that underwent the above defined selected non-cardiac surgery between January 1, 2011 and October 31, 2014 (3 years, 10 months) at our institution were considered for the study. Among these patients (both diabetic and non-diabetic) those who had glucose levels measured during intraoperative and immediate postoperative (first 24 h period after surgery) were further considered for the study. Short duration surgeries (<2 h) and cases in which glucose levels were not frequently monitored (<4 glucose measurements) were excluded from the study. To simplify interpretation of results, patients who had multiple surgeries were excluded from the study. A flow chart that shows the inclusion and exclusion of patients for this study are shown in Fig. 1.

Power calculations were not performed prior to the study and all available surgical procedures documented in the electronic medical record at the time of the study were considered.

Data sources

At our institution, intraoperative anesthesia care is documented through an Anesthesia Information Management System (AIMS). AIMS automatically acquires and documents blood glucose measurements performed by both central laboratory and point of care glucose meters. Patient characteristics such as diabetes status, medication history and postoperative glucose results are documented in a hospital information management system and archived in a data warehouse called AMALGA (Microsoft Inc., Redmond, WA). Postoperative complications were derived from multiple sources such as discharge ICDs (International Classification of Diseases), discharge summary and daily progress notes that detail the hospital course of a patient's stay along with any complications. Other outcome measures such as length of stay, 30-day mortality and readmission were also derived from the Amalga data warehouse.

After IRB approval, both intraoperative and postoperative glucose values, and outcome parameters were retrospectively extracted from the AIMS and AMALGA databases for all the surgical patients that met the inclusion criteria.

Data verification

Though data were first extracted through electronic database queries, it was manually verified for accuracy, and any missing information were extracted from alternate sources in the electronic medical record for all cases that met inclusion criteria. This process provided an accurate and validated dataset for further analysis.

Study outcomes and analysis

The primary study outcome measures were length of stay (both hospital and intensive care unit –ICU), 30-day mortality, in-hospital complications after surgery (infections, cardiac, pulmonary and renal) and 30-day readmission due to surgery complications. The main data analysis focused on determining the association of perioperative mean glucose and glycemic variability with study outcomes. Glycemic variability was defined as the standard deviation of glucose measurements. As a secondary data analysis we explored whether managing mean glucose within three categorized ranges <140 mg/dL, 140-180 mg/dL and >180 mg/dL were incrementally associated with poorer patient outcomes. Similarly, we also explored whether managing glycemic variability within categorized ranges <20 mg/dL, 20-30 mg/dL and >30 mg/dL are incrementally associated with poorer outcomes. The motivation for this secondary analysis was to identify optimal targets for mean glucose levels and glycemic variability to enhance patient outcomes.

Statistical methods

Descriptive statistics for the patient and procedure characteristics are presented as mean $\pm$ SD for continuous variables and as counts

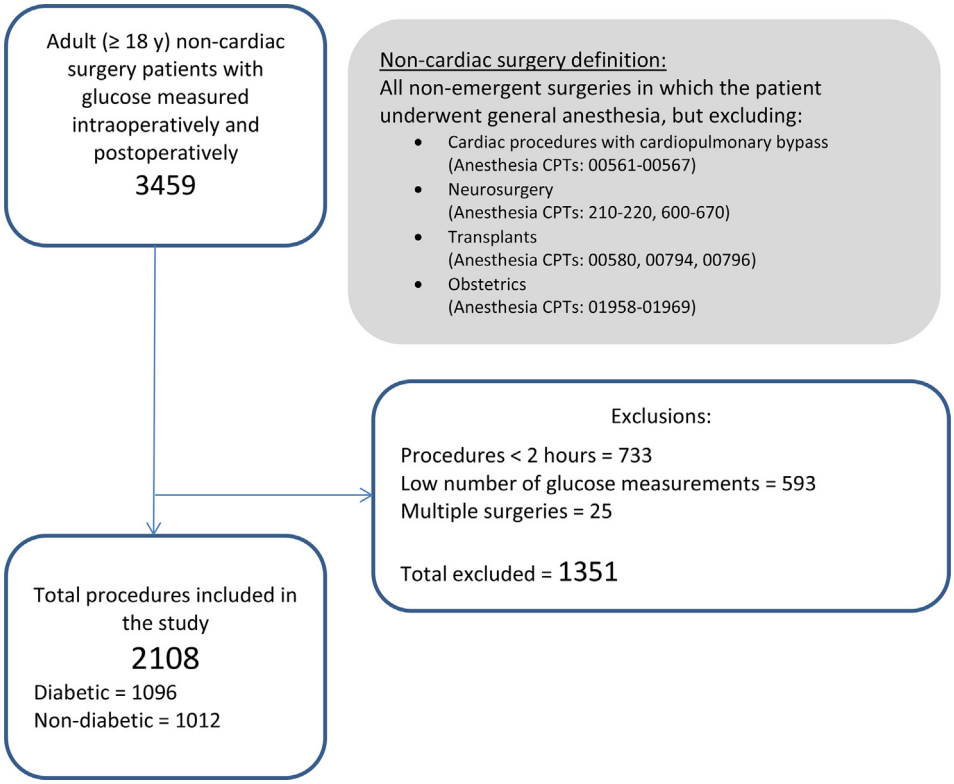


Fig. 1. Study flow chart showing inclusion and exclusion criteria and case counts.

and percentages for categorical variables. Linear regression was used to evaluate the adjusted association of perioperative glucose variables (mean glucose level and glycemic variability, each in a separate model) on continuous patient outcomes (length of stay) while logistic regression evaluated the association on binary outcomes (mortality and complications). All regression models were adjusted for covariates. Covariates were selected by a forward stepwise variable selection technique ($p < 0.05$ for entry) from candidate covariates that included age, BMI, ASA (American Society of Anesthesiology) patient acuity score, procedure duration, and steroid use. Preoperative glucose was also considered as a covariate in diabetic patients. Because patient mortality was encountered only in a few instances in our dataset, Firth's bias-reduced logistic regression was used in place of the traditional logistic regression to estimate the effect on mortality.[33] Linear regression confidence intervals and p-values were calculated using the non-parametric bootstrap method. Logistic regression confidence intervals and p-values were calculated by the profile likelihood method and the likelihood ratio test, respectively. As a sensitivity analysis, we also used linear and logistic regression to evaluate the interaction effect of mean glucose level and glycemic variability on the outcomes (results not shown) and found no statistically non-significant evidence for it.

All calculations were carried out in R, version 3.1.0 (R Foundation for Statistical Computing, Vienna Austria). A p-value <0.05 was used to define statistical significance. All tests were two-sided and were not adjusted for multiple comparisons. Although p-values are presented, the primary focus of this analysis is to estimate the effects of glucose parameters on patient outcome.

Results

A total of 2108 patients (1096 diabetic and 1012 non-diabetic) qualified for the study. Patient and surgery characteristics of procedures included in the study are shown in Table 1. As diabetic and non-diabetic patients were analyzed separately as two distinct cohorts, patient and surgery characteristics were not compared between the groups. However, as shown in Table 1, hemoglobin A1C and body mass index were higher in the diabetic group as expected, while the non-diabetic patients underwent longer duration surgery. The mean glucose levels and glycemic variability were higher in diabetic patients when compared with non-diabetics. None of the patients had severe hypoglycemia (<40 mg/dL). Mean glucose and glycemic variability were strongly correlated (Pearson correlations of 0.62 and 0.45 for the diabetic and non-diabetic patients, respectively).

The adjusted effects of glucose parameters on the outcome are presented separately for diabetic and non-diabetic patients. Unadjusted results presented as supplemental material (Supplemental Table 1).

Length of stay

Table 2 presents the adjusted association between glucose parameters and length of stay. Hospital and ICU length of stays were separately analyzed (Table 2). In diabetic patients, higher glycemic variability was associated with longer hospital length of stay, but not with ICU length of stay. However, in non-diabetic patients, both higher mean glucose levels and glycemic variability were associated with longer hospital and ICU length of stays.

30-day mortality

The adjusted association between glucose parameters and 30-day mortality is shown in Table 3. In diabetic patients, higher glycemic variability was associated with greater risk of mortality while mean glucose levels were not significantly associated with

Table 1
Characteristics of patient, surgery, blood glucose levels and postoperative outcome among the cases included in the study. Intergroup comparison between diabetic and non-diabetic patients was not performed as these two patient groups were considered distinct and the same data analysis was performed for each group separately.

	Diabetic (N = 1096)	Non-diabetic (N = 1012)
	N (%) or mean ± SD	N (%) or mean ± SD
Characteristics of patient and surgery		
ASA	3.0 ± 0.5	2.9 ± 0.6
Age (years)	60.7 ± 12.5	58.2 ± 14.3
BMI	34.8 ± 10.8	29.3 ± 8.6
HbA1C	7.2 ± 1.6 (n = 630)	5.5 ± 0.5 (n = 97)
Procedure duration (hours)	4.6 ± 2.2	5.8 ± 2.6
Intraoperative use of steroids	294 (26.8%)	400 (39.5%)
Perioperative use of insulin	892 (81.4%)	507 (50.1%)
Perioperative use of vasopressors	896 (81.7%)	894 (88.3%)
Characteristics of blood glucose levels		
Number of glucose measurements	17.0 ± 7.4	13.5 ± 7.5
Mean glucose (mg/dL)	157.2 ± 27.4	144.9 ± 18.3
Mean glucose (mg/dL) category		
<140	279 (24.2%)	403 (39.8%)
140-179	697 (60.5%)	576 (56.9%)
≥180	176 (15.3%)	33 (3.3%)
Glycemic variability SD (mg/dL)	34.5 ± 15.8	27.2 ± 15.1
Glycemic variability SD (mg/dL) category		
<20	170 (14.8%)	320 (31.6%)
20–29.95	363 (31.5%)	378 (37.4%)
≥30	619 (53.7%)	314 (31.0%)
Characteristics of postoperative outcome		
Length of stay – Hospital (days)	6.2 ± 7.9	8.8 ± 9.3
Length of stay – ICU (days)	1.3 ± 4.6	1.6 ± 3.7
Death	16 (1.4%)	22 (2.2%)
Any complications	232 (20.1%)	239 (23.6%)
Infection complications	102 (8.9%)	128 (12.6%)
Renal complications	64 (5.6%)	36 (3.6%)
Pulmonary complications	52 (4.5%)	46 (4.5%)
Cardiovascular complications	72 (6.2%)	72 (7.1%)
Readmission	56 (4.9%)	57 (5.6%)

Diabetic N = 1096 and non-Diabetic N = 1012 unless otherwise specified.

mortality. In non-diabetic patients the glucose parameters were not significantly associated with mortality.

Postoperative complications

Table 4 shows the association between glucose parameters and complications. In diabetic patients both higher mean glucose levels and glycemic variability were associated with higher risk of post-surgery complications. In non-diabetic patient, a similar, yet slightly stronger association between glucose parameters and post-surgery complications was observed.

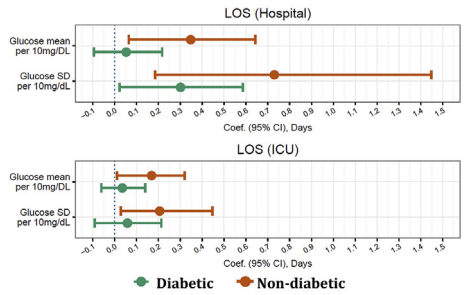
A positive association between glucose parameters and all of the individual postoperative complications were generally observed, though the degree of association varied between different types of complications and patients. Both mean glucose levels and glycemic variability were positively and significantly associated with post-operative infections in non-diabetic patients, but not in diabetic patients. Larger risk of cardiovascular complications with higher mean glucose was observed in diabetic patients. Glycemic variability was positively associated with cardiovascular complications in both diabetic and non-diabetic patients but the effects were only marginally significant. Mean glucose and glycemic variability were positively associated with pulmonary complications in both diabetic and non-diabetic patients (although the glycemic variability association among diabetic patients was not statistically significant). Glucose parameters were positively associated with renal complications, although the effects among non-diabetic patients were weaker and not statistically significant. Mean glucose levels did not significantly influence the risk of readmission. However, in non-diabetic patients, glycemic variability was positively and significantly associated with readmission.

Categorized glucose parameters and outcomes

Table 5 shows the association between categorized glucose parameters and the two primary outcomes, hospital length of stay and postoperative complications. In diabetic patients, a trend for about 1 day longer hospital length of stay was observed for glycemic variability ≥30 mg/dL (compared to glucose SD < 20 mg/dL) and a 50% higher odds of a complications when mean glucose levels ≥ 180 mg/dL, (compared to mean glucose levels < 140 mg/dL) though the latter was not statistically significant. For non-diabetic patients, mean glucose levels ≥180 mg/dL and glycemic variability ≥30 mg/dL were associated with increased length of stay (the latter was marginally significant). Similarly, mean glucose levels 140-179 mg/dL and ≥180 mg/dL (compared to mean glucose levels < 140 mg/dL) and glycemic variability ≥ 30 mg/dL (compared to glucose SD < 20 mg/dL) were associated with significantly greater risks of postoperative complications in non-diabetic patients.

The combined effects of mean glucose and glycemic variability on the mean length of stay and complication rates are illustrated in Fig. 2. In the two-dimensional graphs, the X and Y axes represent categories of mean glucose levels and glycemic variability respectively. The graph is divided into tiles representing combinations of mean glucose and glycemic variability categories. The mean length

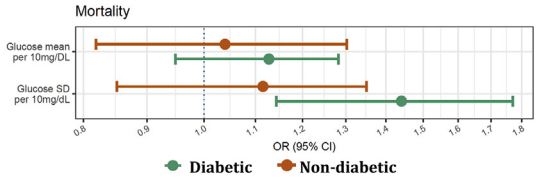
Table 2
Adjusted effects of the glucose parameters on length of stay (LOS) are presented graphically and numerically. Hospital and ICU lengths of stays were separately analyzed. The two glucose parameters (mean glucose and glycemic variability) were tested in separate models and adjustment variables were selected using the forward stepwise variable selection ($p < 0.05$). Statistically significant effects ($p < 0.05$) are shown in bold fonts.



	Diabetic (N = 1096)		Non-diabetic (N = 1012)	
	coef. (95% CI)	p	coef. (95% CI)	p
Hospital				
Mean Glucose	0.06 (−0.09, 0.22)	0.47	**0.29 (0.03, 0.56)**	**0.026**
Glycemic Variability	**0.32 (0.06, 0.61)**	**0.021**	**0.68 (0.17, 1.34)**	**0.004**
ICU				
Mean Glucose	0.03 (−0.06, 0.14)	0.49	**0.18 (0.04, 0.31)**	**0.013**
Glycemic Variability	0.06 (−0.09, 0.21)	0.43	**0.24 (0.07, 0.46)**	**0.003**

Coefficients for mean glucose and glycemic variability are per 10 mg/dL.
Coef. = regression coefficient, CI = Confidence Interval.
Hospital length of stay adjustment variables: procedure duration, ASA (diabetic); procedure duration, BMI, ASA (non-diabetic).
ICU length of stay adjustment variables: procedure duration, ASA, preoperative glucose (diabetic); BMI, ASA (non-diabetic).

Table 3
Adjusted effects of the glucose parameters on 30-day mortality. The two glucose parameters (mean glucose and glycemic variability) were tested in separate models and adjustment variables were selected using the forward stepwise variable selection ($p < 0.05$). Statistically significant effects ($p < 0.05$) are shown in bold fonts.



	Diabetic (N = 1096)		Non-diabetic (N = 1012)	
	OR (95% CI)	p	OR (95% CI)	p
Mean Glucose	1.12 (0.95–1.25)	0.16	0.92 (0.67–1.24)	0.57
Glycemic Variability	**1.42 (1.14–1.71)**	**0.003**	1.16 (0.77–1.68)	0.46

Odds ratios for mean glucose and glycemic variability are per 10 mg/dL.
OR = Odds Ratio, CI = Confidence Interval.
Adjustment variables: ASA (diabetic); ASA (non-diabetic).

of stay and complication rates (95% CI) for each tile is color-coded and is numerically shown within each tile.

For diabetic patients the mean length of stay was lowest when the mean glucose was in the range 140–179 mg/dL with glycemic variability <20 mg/dL. For non-diabetic patients, an increase in length of stay was observed for both greater mean glucose and glycemic variability. In diabetic patients, the lowest rates of complications was seen when the mean glucose <140 mg/dL and glycemic variability 20-30 mg/dL. In non-diabetic patients, lowest complication rates were observed when mean glucose <140 mg/dL and glycemic variability 20-30 mg/dL, with a substantial increase in complication rates for higher mean glucose levels. Overall, the effects of glucose parameters on mean length of stay and complication rates shown in Fig. 2 are more striking among non-diabetic patients while they are diminished among diabetic patients. Finally, we did not find significant interaction between mean glucose levels and glycemic variability which suggests that the effect of mean glucose levels on the outcomes was not significantly modified by glycemic variability and vice versa.

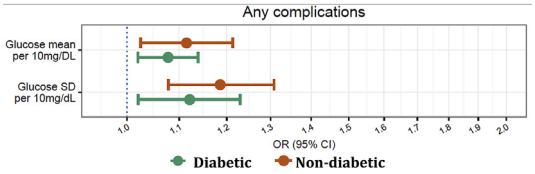
Discussion

Unlike previous studies that focused on subsets of patient populations and types of surgery, we explored the association between glucose parameters and postoperative outcome in all non-cardiac surgeries *separately* for diabetic and non-diabetic patients. Also, unlike previous studies that mostly focused on the postoperative phase, we explored the association of hyperglycemia on outcomes during the most acute phase of surgical care - intraoperative and immediate postoperative periods. Lastly, we explored the association of two glucose parameters, mean glucose levels and glycemic variability, separately on outcome. Through these approaches, we were able to explore the association of hyperglycemia on outcomes in a broad surgical population, while differentiating the results in diabetic and non-diabetic patients. In this large retrospective study on non-cardiac surgery patients, we found that length of stay and postoperative complications are associated with poor perioperative glycemic management. The associations were different for diabetic and non-diabetic patients and also different for various outcome parameters.

The study results show that hyperglycemia and glycemic variability are associated with outcomes differently in diabetic and non-diabetic patients during the acute phase. Interestingly, the association between glucose parameters and outcomes were found stronger in non-diabetic patients when compared with diabetic patients. Specifically, poor glucose management (high mean glucose levels and large glycemic variability) was associated with longer hospital and ICU length of stays and postoperative complications in non-diabetic patients (Table 2). However, the glycemic parameters were only weakly associated in diabetic patients. Further, unlike for non-diabetic patients, ICU length of stay was not associated with glucose parameters in diabetic patients. The reasons for this stronger association in non-diabetic patients is unclear, though these results are in alignment with some recent studies that also report that the poor glycemic management in non-diabetic surgical patients is associated with poor outcomes.[34,35]

Initial enthusiasm on the benefits on tight glucose control (80-110 mg/dL) in critically ill patients[25] was later tempered by the NICE-study[26] which found increased incidences of hypoglycemia and poorer outcome with tight glycemic control. Subsequent studies that explored the ideal perioperative glucose level could not find a definite target range,[12,23,36] leading to believe that optimal targets may vary for different surgical procedures and patient populations. In this study we attempted to identify targets for mean glucose and glycemic variability for optimal outcomes separately for diabetic and non-diabetic patients. We categorized mean glucose levels and glycemic variabilities; and compared the primary outcomes, hospital length of stay and any complications within each category (Table 5). In non-diabetic patients, length of stay and complications are the lowest if mean glucose levels are kept <140 mg/dL and glycemic variability <20 mg/dL. However, a definitive target for diabetic patients could not be identified, though trends suggest a mean glucose level <180 mg/dL and glycemic variability <30 mg/dL would be desirable. These results point

Table 4
Adjusted effects of the glucose parameters on post-surgery complications and readmission due to surgery complications. The two glucose parameters (mean glucose and glycemic variability) were tested in separate models. Adjustment variables for each complication were selected using the forward stepwise variable selection ($p < 0.05$). Statistically significant effects ($p < 0.05$) are shown in bold fonts.3



Complications	Diabetic (N = 1096)		Non-diabetic (N = 1012)	
	OR (95% CI)	p	OR (95% CI)	p
Any complication *(adjustment variables: procedure duration, ASA (diabetic); procedure duration, BMI, ASA, age (non-diabetic)*				
Mean Glucose	**1.07 (1.02, 1.13)**	**0.009**	**1.13 (1.05, 1.23)**	**0.002**
Glycemic Variability	**1.11 (1.01, 1.22)**	**0.021**	**1.20 (1.09, 1.32)**	**<0.001**
Infections (Surgical site, Urinary track, Sepsis, Bacteremia, Pneumonia, Endocarditis, Not otherwise specified) *adjustment variables: procedure duration, ASA (diabetic); procedure duration, BMI, ASA (non-diabetic)*				
Mean Glucose	1.05 (0.97, 1.14)	0.21	**1.13 (1.02, 1.25)**	**0.016**
Glycemic Variability	1.10 (0.96, 1.25)	0.14	**1.21 (1.09, 1.34)**	**<0.001**
Cardiovascular (Stroke, Myocardial infraction, Ischemia, Arrhythmia, atrial fibrillation, Not otherwise specified) *adjustment variables: ASA, age, steroid use (diabetic); BMI, age (non-diabetic)*				
Mean Glucose	**1.11 (1.03, 1.20)**	**0.004**	1.08 (0.95, 1.22)	0.25
Glycemic Variability	1.14 (0.99, 1.29)	0.067	1.12 (0.97, 1.26)	0.094
Pulmonary (Respiratory failure, Prolonged ventilator support, Reintubation, Not otherwise specified) *adjustment variables: procedure duration, ASA, BMI, steroid use (diabetic); ASA, BMI (non-diabetic)*				
Mean Glucose	**1.12 (1.01, 1.23)**	**0.025**	**1.21 (1.04, 1.39)**	**0.012**
Glycemic Variability	1.18 (0.99, 1.39)	0.052	**1.16 (0.99, 1.33)**	**0.045**
Renal (Hemodialysis, Creatinine increase, Acute tubular necrosis increase, Not otherwise specified) *adjustment variables: procedure duration, ASA, BMI (diabetic); ASA (non-diabetic)*				
Mean Glucose	**1.15 (1.06, 1.25)**	**<0.001**	1.14 (0.96, 1.34)	0.12
Glycemic Variability	**1.42 (1.24, 1.62)**	**<0.001**	1.11 (0.91, 1.29)	0.26
Readmission due to surgery complications *(adjustment variables: none (diabetic); steroid use (non-diabetic)*				
Mean Glucose	1.03 (0.93, 1.13)	0.49	1.10 (0.95, 1.26)	0.19
Glycemic Variability	0.95 (0.78, 1.13)	0.58	**1.16 (1.00, 1.32)**	**0.027**

Coefficients and for mean glucose and glycemic variability are per 10 mg/dL.
OR = Odds Ratio, CI = Confidence Interval.

Table 5
Adjusted effects of the categorized mean glucose levels and glycemic variabilities on the primary outcomes (hospital length of stay and any complications).

	Diabetic (N = 1096)		Non-diabetic (N = 1012)	
Hospital Length of Stay	coef. (95% CI)	*p*	coef. (95% CI)	*p*
Mean Glucose <140 mg/dL	0.00 (ref.)		0.00 (ref.)	
Mean Glucose 140–179 mg/dL	0.60 (−0.32, 1.53)	0.21	**1.40 (0.28, 2.54)**	**0.013**
Mean Glucose ≥180 mg/dL	0.53 (−0.74, 1.87)	0.43	−0.01 (−1.97, 1.98)	0.97
Glucose SD < 20	0.00 (ref.)		0.00 (ref.)	
Glucose SD 20–29.95	0.69 (−0.38, 1.82)	0.22	−0.04 (−1.21, 1.05)	0.99
Glucose SD ≥ 30	**0.99 (0.05, 1.91)**	**0.040**	1.48 (−0.04, 3.08)	0.057
Any Complications	OR (95% CI)	*p*	OR (95% CI)	*p*
Mean Glucose <140 mg/dL	1.00 (ref.)		1.00 (ref.)	
Mean Glucose 140–179 mg/dL	1.26 (0.86, 1.86)	0.24	**1.55 (1.12, 2.14)**	**0.008**
Mean Glucose ≥180 mg/dL	1.54 (0.92, 2.57)	0.098	**2.26 (1.02, 4.81)**	**0.038**
Glucose SD < 20	1.00 (ref.)		1.00 (ref.)	
Glucose SD 20–29.95	0.79 (0.49, 1.29)	0.33	1.14 (0.78, 1.67)	0.51
Glucose SD ≥ 30	0.90 (0.58, 1.42)	0.63	**1.76 (1.21, 2.57)**	**0.003**

Coef. = regression coefficient, OR = Odds Ratio, CI = Confidence Interval.
The two glucose variables (mean glucose and glycemic variability) were tested in separate models.
Adjustment variables were selected using the forward stepwise variable selection ($p < 0.05$). See Tables 2 and 4 for selected adjustment variables.

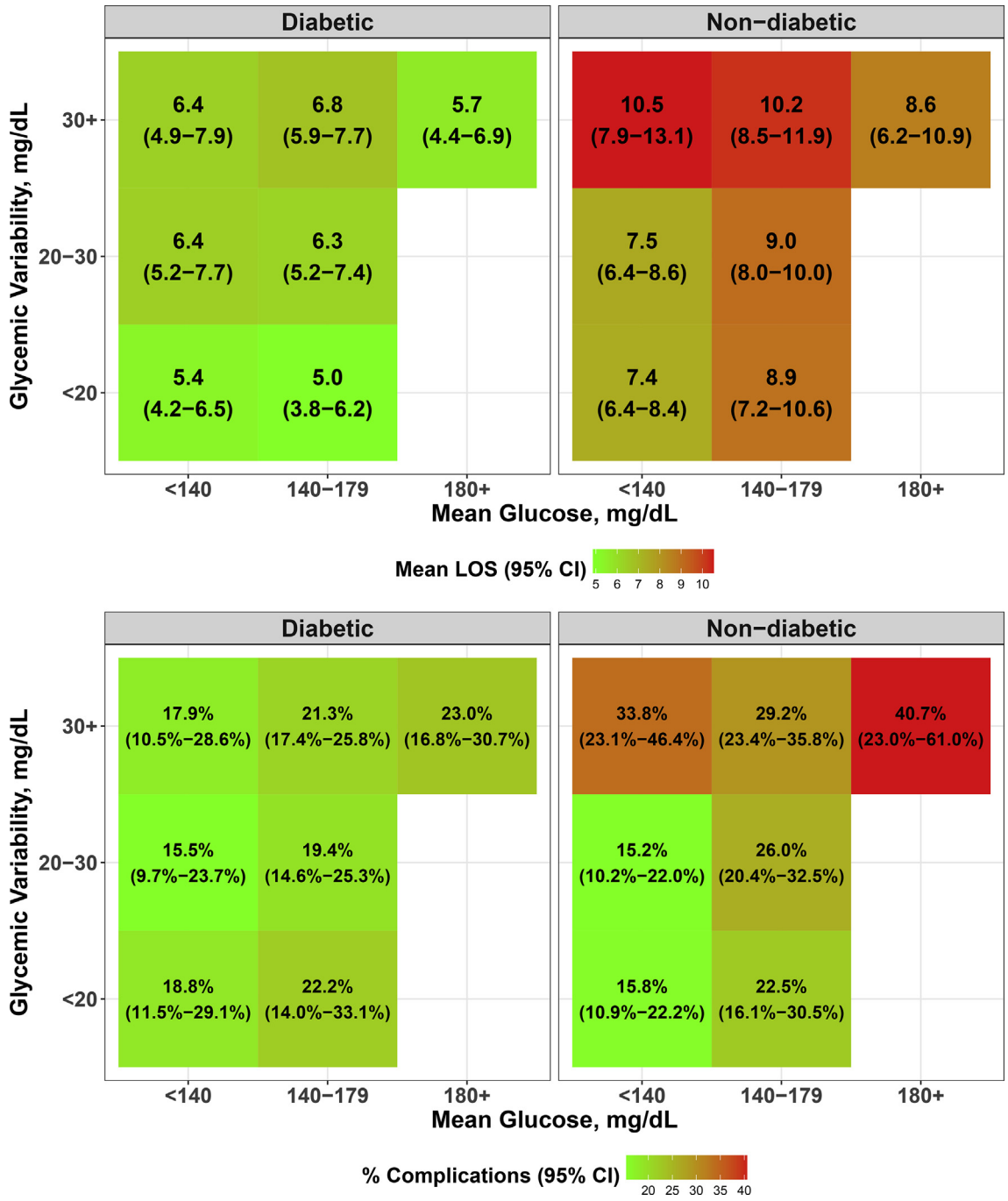


Fig. 2. The joint effect of mean glucose levels (X axis) and glycemic variability (Y axis) on the mean length of stay and postoperative complication rates. Mean length of stay and complication rate (95% CI) for each combination of mean glucose category and glycemic variability category are shown and color-coded. Results for combinations of mean glucose and glycemic variability that contained 20 or fewer patients were excluded. The sample sizes for the shown data points range from 27 to 389 procedures.

to a recommendation to start insulin treatment at a threshold of 140 mg/dL and to closely monitor and manage glucose levels to keep glycemic variability to <20 mg/dL in non-diabetic patients. However, a more liberal approach may be adopted with diabetic patients. Though these results need to be prospectively confirmed through randomized studies, close perioperative control of glucose levels in non-diabetic patients will be a significant shift in current practice of managing non-diabetic non-cardiac surgery patients. The potential benefit of controlling hyperglycemia below 140 mg/dL should be balanced against the risk of hypoglycemia and its deleterious implications, particularly in the anesthetized patients in whom it may be difficult to detect this condition without close glucose monitoring.

This study highlights associations between glucose levels and outcome. It should be clarified that associations may not insinuate causality and hence the study results may not portray direct effect of glucose parameters on outcome. Even if we assumed the joint effect of the two glucose parameters is causal it is challenging to establish which of the inter-related parameters causes the outcomes. It should also be noted that even if some of the confidence

intervals are relatively broad (for example, associations of glycemic variability with cardiovascular and pulmonary complications in diabetic patients) to warrant statistical significance, the associations may still have clinical significance.

The primary limitation of this study is its retrospective nature and any potential bias. Though we utilized a fairly large sample size and adjusted for available potential confounders, residual confounding is plausible, and the effects of the glycemic control variables on the outcomes could theoretically be attributed to unknown confounding factors. For example, confounders such as infection, blood loss, degree of tissue damage and concomitant organ dysfunction could have potentially influenced glucose levels and outcome. The inclusion criteria may have caused selection bias though they were chosen such that a reasonably uniform, yet sufficiently broad set of non-cardiac surgery cases were selected. Another limitation is the single center nature of the study, though our hospital system is representative of a typical tertiary academic medical center. Whether the results have broader representation needs to be explored through multi-institutional studies.

Conclusion

This study explored the association between *acute phase* perioperative glucose parameters and postoperative outcomes after selected non-cardiac surgery in diabetic and non-diabetic patients. In diabetic patients, higher glycemic variability was associated with a longer length of stay, higher risk of mortality and of complications. However, mean glucose levels were not associated with length of stay and mortality. In non-diabetic patients, higher mean glucose levels and glycemic variability were both associated with longer length of stay and higher risk of complications. When glucose means and variabilities were grouped into categories among non-diabetic patients, the group with mean glucose levels below 140 mg/dL and glycemic variability less than 20 mg/dL was associated with the lowest length of stay and complication rates. However, a distinct range of glucose parameters associated with lowest length of stay and complication rates could not be identified for diabetic patients. These results suggest that diabetic and non-diabetic patients show different glycemic response to surgery and anesthesia, and likely require different glycemic management strategies including different glucose targets. Prospective randomized clinical trials are needed to validate these results.

Authorship

Study concept and design: *BN, MH*. Acquisition, analysis, or interpretation of data: *All authors*.

Drafting the manuscript

BN, MN, MH. Critical revision of the manuscript for important intellectual content: *All authors*. Statistical analysis: *MN*. Administrative, technical, or material support: *BN, MH*.

Study supervision

BN, MH.

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Disclosures

Bala G. Nair holds equity in Perimatics LLC unrelated to this study. Other authors have no conflict of interest.

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Appendix A. Supplementary data

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