Hyperglycemia Is Associated with Increased Risk of Morbidity and Mortality after Colectomy for Cancer

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BACKGROUND: The relationship of hyperglycemia to general surgery outcomes is not well-understood. We studied the association of operative day and postoperative day 1 (POD1) blood glucose (BG) with outcomes after open colectomy for cancer.

STUDY DESIGN: We retrospectively analyzed the 2000-2005 Veterans Affairs Surgical Quality Improvement Program database, linked with Veterans Affairs Decision Support System BG values. Median BG was categorized as hypoglycemic (<80 mg/dL); normoglycemic (BG 80−120 mg/dL); or mildly (BG 121−160 mg/dL), moderately (BG 161−200 mg/dL), or severely (BG >200 mg/dL) hyperglycemic. The relationship of BG to postoperative outcomes was assessed with multivariable logistic regression.

RESULTS: We identified 9,638 colectomies. We excluded 511 procedures for emergency status or preoperative coma, mechanical ventilation, or sepsis. After excluding patients without recorded BG, we analyzed operative day and POD1 BG in 7,576 and 5,773 procedures, respectively. On multivariable analysis, operative day moderate hyperglycemia was associated with surgical site infection (odds ratio = 1.44; 95% CI, 1.10−1.87). POD1 severe hyperglycemia was associated with cardiac arrest (odds ratio = 2.31; 95% CI, 1.08−4.98) and death (odds ratio = 1.97; 95% CI, 1.23−3.15). POD1 mild (odds ratio = 2.20; 95% CI, 1.05−4.60), moderate (odds ratio = 3.44; 95% CI, 1.51−7.84), and severe (odds ratio = 3.94; 95% CI, 1.64−9.58) hyperglycemia and hypoglycemia (odds ratio = 6.74; 95% CI, 1.75−25.97) were associated with myocardial infarction. Associations were similar in diabetic and nondiabetic patients.

CONCLUSIONS: Even mild hyperglycemia was associated with adverse outcomes after colectomy, suggesting that a perioperative BG target of 80 to 120 mg/dL, although avoiding hypoglycemia, might be appropriate. Randomized clinical trials are needed to confirm these findings. (J Am Coll Surg 2012;214:68–80. © 2012 by the American College of Surgeons)

Perioperative hyperglycemia is a common phenomenon after major general surgery, affecting an estimated 24% to 72% of diagnosed diabetic patients and 20% to 46% of patients without known diabetes.[1-5] The physiologic stress of major surgery can initiate a complex cascade of responses that result in hyperglycemia. Surgery promotes the release of counter-regulatory hormones, including glucagon, epinephrine, norepinephrine, glucocorticoids, and growth hormone. These lead to elevated blood glucose (BG) levels, through both increased glucose production (via accelerated gluconeogenesis, glycogenolysis, and lipolysis) and decreased glucose use (via skeletal muscle insulin resistance). Colorectal surgery can also induce hyperglycemia by exposing the patient's immune system to endotoxin from gram-negative bacterial cell walls. Subsequent release of tumor necrosis factor−α from mononuclear cells results in insulin resistance in the liver and skeletal muscle, augmenting stress-induced hyperglycemia.[6]

In 2001, the pivotal Leuven surgical trial drew attention to the importance of glycemic control in improving outcomes in critically ill surgical patients,[7] although subsequent studies have suggested that more liberal glycemic targets than the strict range (80 to 110 mg/dL) advocated in the Leuven trials might be most appropriate.[8,9] Focus on the association of hyperglycemia with outcomes in critically ill patients has generated interest in the importance of hyperglycemia in other disease states, including surgical

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Abbreviations and Acronyms

BG = blood glucose
MICU = medical ICU
OD = operative day
POD1 = postoperative day 1
SICU = surgical ICU
SSI = surgical site infection
UTI = urinary tract infection
VA = Veterans Affairs
VASQIP = Veterans Affairs Surgical Quality Improvement Program
VTE = venous thromboembolism

outcomes. Although the association of perioperative hyperglycemia with adverse outcomes after cardiac surgery is well-established,[10-15] the relationship of hyperglycemia to outcomes after general surgery is not as well-understood. In particular, few studies have focused on the relationship between perioperative hyperglycemia and colorectal surgery outcomes. Three small, single-center studies of diabetic patients undergoing colorectal surgery reported an association between perioperative hyperglycemia and surgical site infection (SSI).[1,16,17] However, the importance of perioperative hyperglycemia in nondiabetic patients undergoing colectomy and the relationship between perioperative hyperglycemia and noninfectious outcomes has received little attention.

We undertook a study to examine the association between perioperative BG level and 30-day outcomes after elective colectomy for colon cancer. We limited our study to elective colectomy for cancer because many patients who undergo colectomy for other indications (eg, perforated diverticulitis) have emergency procedures and might experience stress-induced hyperglycemia due to factors other than the surgery itself, such as preoperative sepsis.

METHODS

The Washington, DC Veterans Affairs (VA) Medical Center Institutional Review Board approved this study.

Data acquisition and patient selection

We undertook a retrospective analysis of the VA Surgical Quality Improvement Program (VASQIP) database. The VASQIP database is a repository of information, including perioperative variables and 30-day postoperative outcomes, from patients who underwent major surgery at any of 123 VA Medical Centers that perform major surgery. Trained nurse reviewers prospectively record patient data from physician interview, concurrent chart review, and patient follow-up. Deaths are verified against the VA Beneficiary Identification and Records Locator System death records.[18]

Perioperative blood glucose recordings were determined from the VA Decision Support System and were linked to the records in the VASQIP database using scrambled Social Security numbers. For each patient, median BG values were separately recorded for the operative day (OD) and postoperative day 1 (POD1). Scrambled Social Security numbers were then stripped from the linked VASQIP–Decision Support Services database.

We included all open colectomy procedures with a primary diagnosis of colon cancer from January 1, 2000 to December 31, 2005. Colectomy was defined using CPT codes (Appendix), and colon cancer diagnosis was defined as ICD-9 codes 153 to 154.1. To restrict our analysis to elective colectomy, we excluded any emergent procedure or procedures in patients who had preoperative coma, preoperative mechanical ventilation, or preoperative sepsis. For each day analyzed, we also excluded any procedure without recorded BG on that day.

Blood glucose and adjustment variable definitions

For each day analyzed, we categorized BG as hypoglycemic (BG $<$80 mg/dL), normoglycemic (BG 80 to 120 mg/dL), mildly hyperglycemic (BG 121 to 160 mg/dL), moderately hyperglycemic (BG 161 to 200 mg/dL), or severely hyperglycemic (BG $>$200 mg/dL).

Comorbidities used in the analysis were recorded in the VASQIP as binary or categorical variables. For the present study, patients treated with oral hypoglycemic medication or insulin were considered diabetic. Patients with diet-controlled diabetes were categorized with nondiabetic patients because these patients are not differentiated in the VASQIP. Current smoking was defined as smoking within 1 year before surgery, and current ethanol abuse was defined as $\geq$2 drinks daily during the 2 weeks before surgery. Partially dependent status was defined as requiring assistance from another person for some activities of daily living, and totally dependent status was defined as requiring assistance for all activities of daily living.

Outcomes

Primary outcomes were death, cardiac arrest, MI, and SSI. Secondary outcomes were respiratory complications, venous thromboembolism (VTE), urinary tract infection (UTI), and sepsis. Cardiac arrest, MI, UTI, and sepsis are predefined VASQIP variables. The remaining outcomes were defined as composites of VASQIP predefined variables. SSIs were defined as superficial or deep wound infection or organ/space infection. Respiratory complications were defined as unplanned reintubation, failure to wean from mechanical ventilation for $>$48 hours, or pneumo-

nia. VTEs were defined as deep venous thrombosis or pulmonary embolism.

Statistical analysis

All analyses were performed separately for each perioperative day. Baseline characteristics were compared across BG categories, using the chi-square statistic for binary and categorical variables and two-tailed ANOVA for continuous variables. Incidence rates for each prespecified complication were calculated within each BG category and compared using the chi-square statistic.

Multivariable logistic regression was used to assess the independent relationship of BG to each study outcome. From among the baseline characteristics considered (Tables 1, 2, and 3), backwards stepwise regression with an exit criterion of $p > 0.1$ was used to select variables for final model inclusion. BG category was forced into the model.

Interaction analyses to assess for effect modification between diabetes and BG level were performed for any outcomes that were significantly associated with BG level in the multivariable models. This was completed using stepwise regression as described here, with BG category, diabetes, and the interaction of diabetes and BG category forced into the model. Subgroup analyses were used to examine any statistically significant interaction term.

RESULTS

A total of 9,638 colectomy procedures for cancer were identified. After applying exclusion criteria (Fig. 1), 7,576 procedures were analyzed for the effect of operative day BG and 5,773 procedures were analyzed for the effect of postoperative day 1 BG. In the assessment of operative day BG, 0.5% were hypoglycemic, 21.3% were normoglycemic, 46.5% were mildly hyperglycemic, 19.1% were moderately hyperglycemic, and 12.7% were severely hyperglycemic. In the assessment of POD1 BG, 1.7% were hypoglycemic, 34.2% were normoglycemic, 41.0% were mildly hyperglycemic, 13.5% were moderately hyperglycemic, and 9.6% were severely hyperglycemic. On each perioperative day, diabetics had a higher incidence and increased severity of hyperglycemia compared with nondiabetics (Fig. 2). However, for both diabetics and nondiabetics, the majority of patients experienced both operative day and POD1 hyperglycemia.

Baseline characteristics, compared across OD and POD1 BG categories, are displayed in Tables 1, 2, and 3. With increasing BG category, the proportion of patients who currently smoked or abused ethanol decreased. Increasing BG category was also associated with increasing prevalence of American Society of Anesthesiologists class 4 to 5. OD hyperglycemia was associated with increased

Table 1. Preoperative Demographics and Behaviors, by Operative Day and Postoperative Day 1 Blood Glucose Category

	Operative day						Postoperative day 1					
	Hypo (n = 40)	Normo (n = 1,610)	Mild hyper (n = 3,520)	Moderate hyper (n = 1,447)	Severe hyper (n = 959)	p Value	Hypo (n = 95)	Normo (n = 1,976)	Mild hyper (n = 2,369)	Moderate hyper (n = 779)	Severe hyper (n = 554)	p Value
Age, y, mean	67.3	67.5	69.4	70.9	69.7	<0.001	68.4	68.4	70.1	70.6	69.8	<0.001
Race, %						0.067						<0.001
Caucasian	75.0	75.9	75.9	75.8	72.6		57.5	71.2	76.1	74.3	74.6	
African American	21.9	17.9	18.1	17.6	17.6		37.9	22.6	17.1	18.2	17.2	
Hispanic	3.1	5.7	5.5	6.2	8.6		4.6	5.7	6.5	6.4	7.4	
Other	0	0.5	0.5	0.4	1.2		0	0.5	0.3	1.2	0.8	
Female sex, %	0	1.9	2.0	1.4	1.9	0.548	1.1	1.6	2.0	1.9	1.8	0.853
Current smoking, %	42.5	30.5	23.4	17.3	14.8	<0.001	35.8	29.7	20.6	17.3	15.9	<0.001
Current ethanol abuse, %	7.5	12.3	11.3	8.2	7.1	<0.001	12.6	12.8	10.2	9.9	6.9	0.001

Hyper, hyperglycemia; Hypo, hypoglycemia; Normo, normoglycemia.

Table 2. Patient Comorbidities by Operative Day and Postoperative Day 1 Blood Glucose Category

	Operative day						Postoperative day 1					
Comorbidity	Hypo (n = 40), %	Normo (n = 1,610), %	Mild hyper (n = 3,520), %	Moderate hyper (n = 1,447), %	Severe hyper (n = 959), %	*p* Value	Hypo (n = 95), %	Normo (n = 1,976), %	Mild hyper (n = 2,369), %	Moderate hyper (n = 779), %	Severe hyper (n = 554), %	*p* Value
CVA, without neurologic deficit	5.0	2.9	3.9	3.1	4.3	0.251	6.3	2.8	3.9	4.8	4.5	0.039
CVA, with neurologic deficit	5.0	4.5	4.2	4.9	6.2	0.149	5.3	5.2	5.0	5.1	6.7	0.622
TIA	0	2.6	3.8	2.6	3.1	0.072	4.2	3.6	3.3	2.6	3.6	0.706
Treated diabetes, oral medication	10.0	5.6	10.3	29.5	43.8	<0.001	8.4	5.8	13.8	38.0	42.2	<0.001
Treated diabetes, insulin	7.5	2.5	3.6	11.7	29.7	<0.001	3.2	2.8	4.7	16.3	34.1	<0.001
COPD	20.0	15.6	15.5	15.4	10.6	0.002	19.0	16.4	15.6	15.8	13.4	0.437
Dyspnea at rest	17.5	17.2	17.5	17.0	17.2	0.903	24.5	18.1	18.7	18.5	18.7	0.044
Dyspnea on exertion	0	1.0	1.2	1.3	1.7	0.903	1.1	1.5	0.9	2.6	2.2	0.044
Dependent, partially	10.0	6.3	6.2	7.5	7.6	0.298	8.4	6.7	7.6	7.6	9.9	0.389
Dependent, totally	0	1.1	0.7	0.8	1.3	0.298	1.1	1.0	1.1	0.8	1.4	0.389
Acute renal failure	0	0.3	0.3	0.4	0.4	0.873	0	0.5	0.1	0.9	0.7	0.010
Dialysis-dependent	0	0.6	0.2	0.3	0.5	0.310	0	0.7	0.2	0.5	0.5	0.161
Infected wound	0	1.4	0.9	1.5	2.7	0.001	0	1.1	1.9	1.7	2.2	0.114
Weight loss	25.0	13.5	10.8	11.7	11.7	0.006	23.2	14.3	12.0	9.6	11.7	<0.001
Disseminated cancer	7.5	8.0	8.1	8.2	7.3	0.942	9.5	8.7	8.7	8.1	8.8	0.982
Chemotherapy	0	1.4	1.2	1.5	2.4	0.096	2.1	1.9	1.5	1.7	2.2	0.785
Radiation	2.5	1.9	2.5	1.9	2.8	0.439	3.2	2.5	2.8	2.7	2.0	0.843
Steroid	2.5	1.8	1.7	1.9	2.6	0.412	1.1	1.6	1.7	2.2	3.6	0.034
CHF	2.5	2.2	2.5	2.5	4.0	0.074	0	2.3	2.9	3.2	5.6	0.001
Ascites	2.5	1.5	1.0	0.7	1.0	0.239	1.1	1.8	0.9	1.5	1.1	0.167
Pneumonia	0	0.3	0.3	0.4	0.4	0.951	1.1	0.2	0.3	0.5	0.4	0.507
Bleeding disorder	2.5	3.6	3.3	4.1	3.8	0.689	8.4	3.8	3.7	4.6	3.3	0.121

CHF, congestive heart failure; Hyper, hyperglycemia; Hypo, hypoglycemia; Normo, normoglycemia; TIA, previous transient ischemic attack.

Table 3. Preoperative Laboratory and Procedure Characteristics by Operative Day and Postoperative Day 1 Blood Glucose Category

	Operative day						Postoperative day 1					
	Hypo (n = 40)	Normo (n = 1,610)	Mild hyper (n = 3,520)	Moderate hyper (n = 1,447)	Severe hyper (n = 959)	*p* Value	Hypo (n = 95)	Normo (n = 1,976)	Mild hyper (n = 2,369)	Moderate hyper (n = 779)	Severe hyper (n = 554)	*p* Value
Laboratory, mean												
Creatinine, mg/dL	1.1	1.1	1.1	1.2	1.2	0.001	1.2	1.1	1.1	1.2	1.2	0.032
Hematocrit, %	36.4	37.6	37.8	37.2	37.1	0.001	36.3	37.5	37.5	37.0	37.1	0.062
Platelets × 1,000 cells/mL	310	283	274	267	271	<0.001	291	284	273	266	267	<0.001
WBC × 1,000 cells/mL	7.7	7.6	7.5	7.6	7.8	0.178	8.3	7.6	7.6	7.6	7.8	0.138
Procedure, %												
ASA class						<0.001						<0.001
1–2	30.0	26.9	22.8	18.6	13.5		20.0	25.6	20.0	14.3	13.0	
3	70.0	62.7	66.9	69.7	74.2		67.4	64.2	68.5	74.2	72.0	
4–5	0	10.4	10.3	11.7	12.3		12.6	10.2	11.5	11.6	15.0	
General anesthesia, %	100	98.8	99.3	99.5	99.4	0.204	97.9	98.9	99.4	99.4	99.1	0.325
Cancer location, %						0.798						0.277
Cecum	20.0	12.2	11.8	13.0	10.7		8.4	11.1	12.5	10.1	11.2	
Appendix	0	0.4	0.3	0.1	0.1		1.1	0.1	0.3	0.4	0	
Ascending colon	20.0	17.6	17.5	17.9	17.0		14.7	16.5	18.5	17.3	16.8	
Transverse colon	12.5	13.2	13.6	14.6	13.7		14.7	13.4	13.3	13.9	11.4	
Sigmoid colon	25.0	25.8	25.0	23.5	25.3		21.1	26.1	23.7	13.9	26.5	
Rectum	12.5	7.5	7.8	8.5	8.1		6.3	8.0	7.7	14.1	10.1	
Colon, other or unspecified	10.0	23.4	24.0	22.4	25.0		33.7	24.8	24.0	24.4	24.0	
Stoma placement, %	12.5	11.9	12.3	12.7	14.5	0.386	19.0	13.5	12.5	11.8	15.9	0.071

ASA, American Society of Anesthesiologists; Hyper, hyperglycemia; Hypo, hypoglycemia; Normo, normoglycemia.

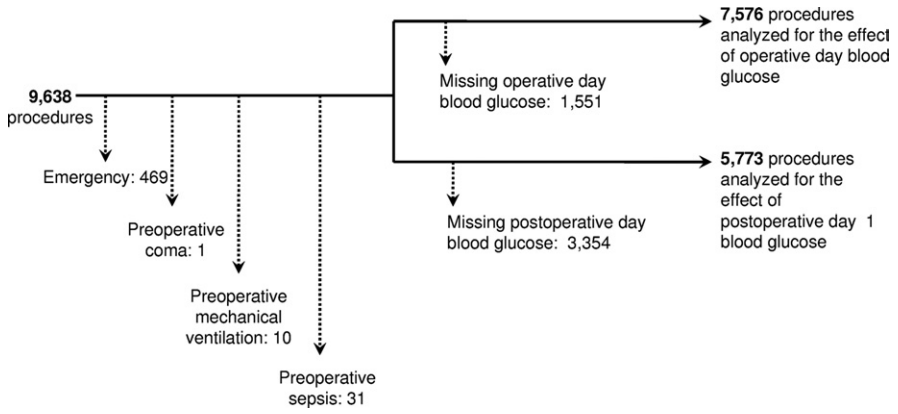

Figure 1. Procedure inclusion and exclusion.

prevalence of preoperative wound infection, and operative day hypoglycemia was associated with increased prevalence of preoperative weight loss and COPD. POD1 hyperglycemia was associated with steroid use and congestive heart failure, and hypoglycemia was associated with previous CVA without residual neurologic deficit, dyspnea, and weight loss.

On unadjusted analysis, increasing OD BG level was associated with increasing incidence of mortality, MI, and respiratory complications. There was a trend-level association between BG level and the need for operative reintervention, which was highest in hypoglycemic and severely hyperglycemic patients (Fig. 3). POD1 BG level had a U-shaped relationship with mortality, MI, cardiac arrest, and UTI, with increased incidence of these complications in hypoglycemic and hyperglycemic patients. POD1 BG level also had a trend-level association with increased risk of respiratory complications (Fig. 4).

On multivariable analysis (Tables 4 and 5), OD moderate hyperglycemia was associated with a 44% increased risk for SSIs. Moderate and severe hyperglycemia were associated with 37% and 55% increases in the risk of respiratory complications, respectively. Severe hyperglycemia was also associated with a 37% increase in risk for operative reinter-

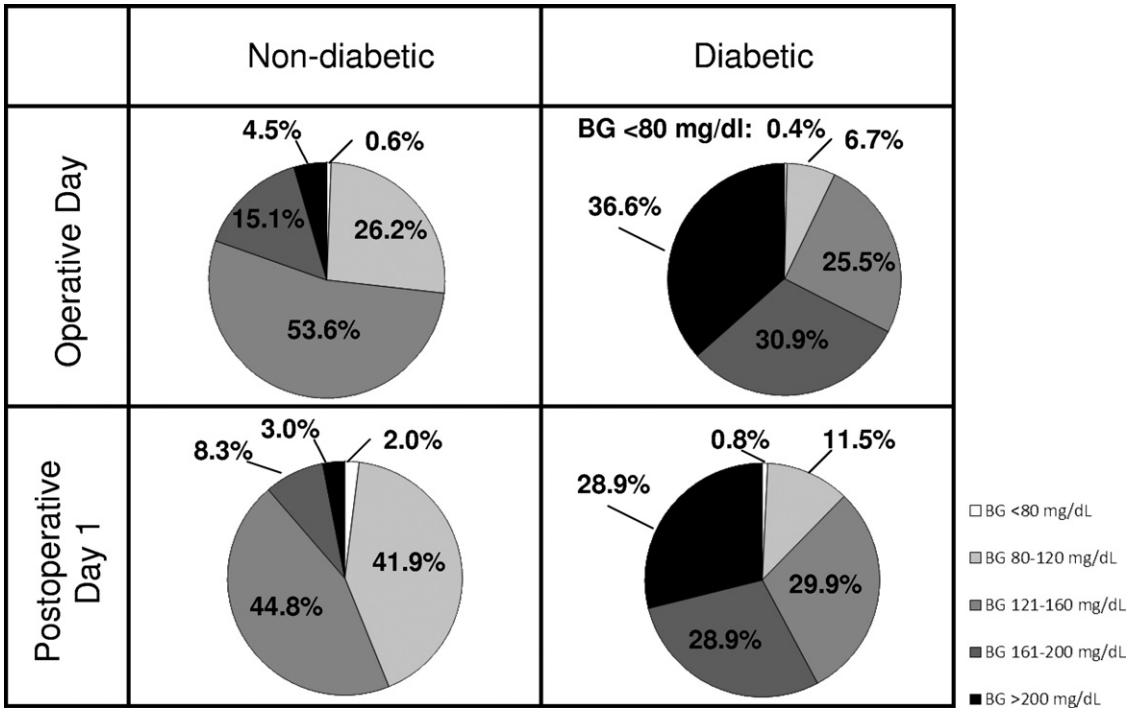

Figure 2. Blood glucose (BG) distribution, by diabetic status and perioperative day.

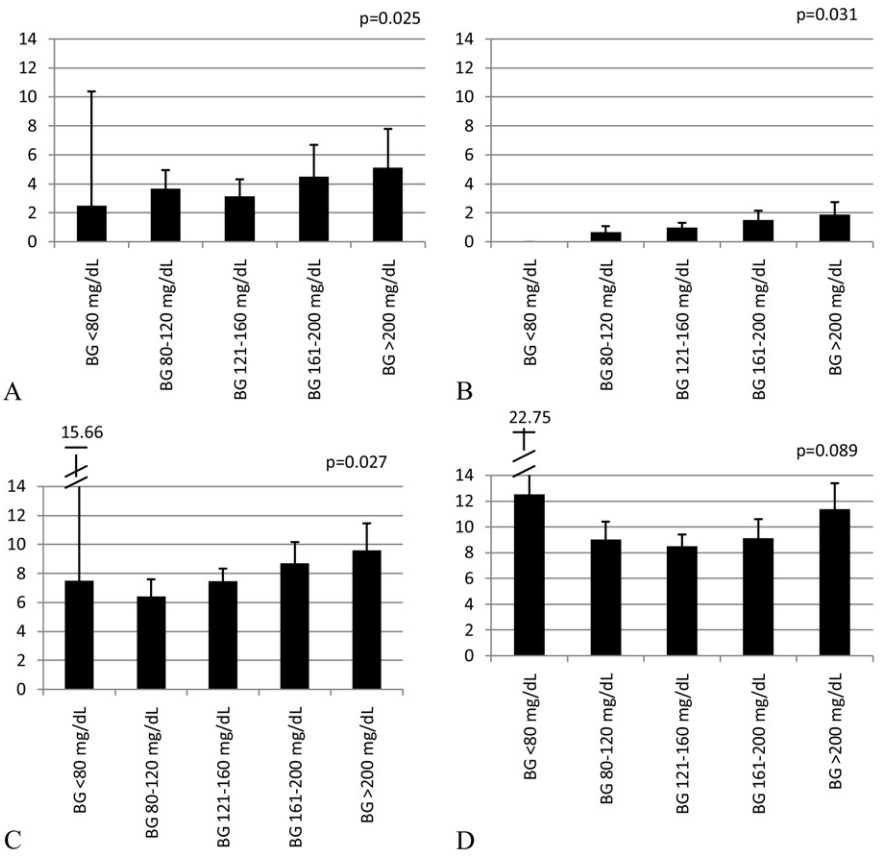

Figure 3. Unadjusted incidence (%) of (A) mortality, (B) MI, (C) respiratory complications, and (D) operative reintervention, by operative day blood glucose level. *p* Values from chi-square analysis are given and outcomes with $p < 0.1$ are shown.

vention. POD1 severe hyperglycemia was independently associated with a 2-fold increase in the risk of death, cardiac arrest, and VTE. Mild, moderate, and severe hyperglycemia were each associated with a >2-fold increase in the risk of MI. Hypoglycemia was independently associated with MI and operative reintervention.

There were no significant interactions between diabetes diagnosis and BG level, indicating that the associations of hypoglycemia and hyperglycemia with study outcomes were similar between diabetic and nondiabetic patients.

DISCUSSION

This study identified an independent association between perioperative hyperglycemia and increased risk of death, cardiac arrest, MI, SSIs, respiratory complications, UTIs, and VTE after colectomy for cancer. Hypoglycemia was associated with MI and operative reintervention. The association of each of these outcomes with BG level was similar for diabetic and nondiabetic patients.

As anticipated, perioperative hyperglycemia was associated with diagnosed diabetes, although even among nondiabetics the majority of patients were hyperglycemic. More surprisingly, both smoking and COPD were negatively correlated with increasing BG level, with the lowest prevalence of smoking and COPD in the most severely hyperglycemic patients. This negative association might be attributable to the negative association of smoking with obesity,[19,20] which is closely associated with diabetes. If fewer smokers were obese and diabetic, a lower incidence of perioperative hyperglycemia in smokers, compared with nonsmokers, would be expected.

Strict glycemic control first received attention in the field of critical care, where conflicting results from randomized clinical trials have generated controversy about its potential benefits and harms. The Leuven surgical trial, published in 2001, reported that strict glycemic control (BG target 80 to 110 mg/dL) was associated with reduced mortality in surgical ICU (SICU) patients.[7] The same investigators subsequently found that strict glycemic control increased the occurrence of hypoglycemic episodes without

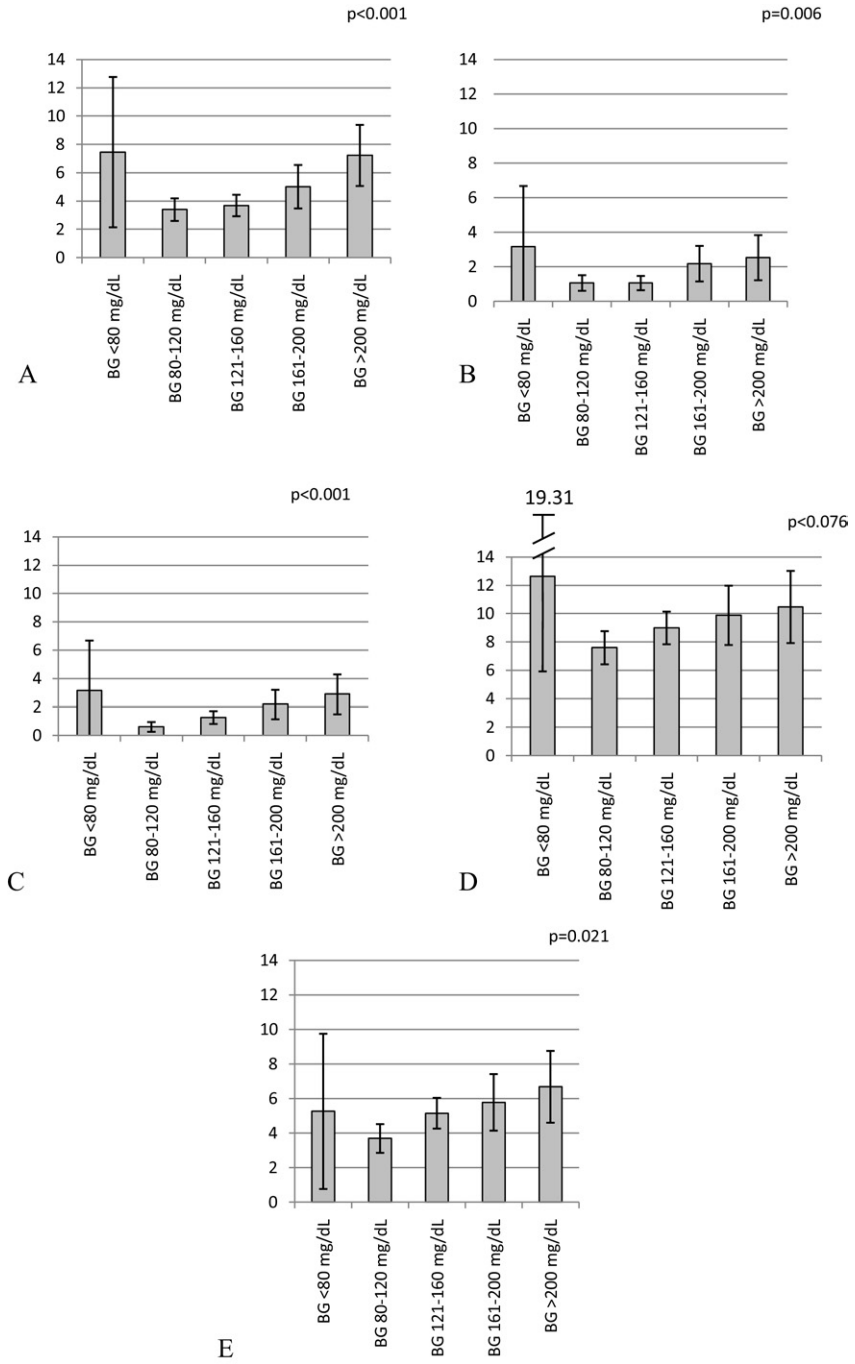

Figure 4. Unadjusted incidence (%) of of (A) mortality, (B) cardiac arrest, (C) MI, (D) respiratory complications, and (E) urinary tract infection, by postoperative day 1 blood glucose level. *p* Values from chi-square analysis are given and outcomes with $p < 0.1$ are shown.

affecting mortality in medical ICU (MICU) patients.[21] More recently, the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, carried out in a cohort of combined SICU and MICU patients, demonstrated that strict glycemic control increased the risk of both hypoglycemia and mortality.[8] A meta-analysis of 26 randomized clinical trials, including the Leuven and NICE-SUGAR trials, found no mortality benefit from strict glycemic control. However, separate analyses by MICU vs SICU setting

Table 4. Adjusted Risk of Study Outcomes, by Blood Glucose Category and Perioperative Day

	Hypoglycemia, BG <80 mg/dL, odds ratio (95% CI)	Normoglycemia, BG 80–140 mg/dL, reference	Mild hyperglycemia, BG 121–160 mg/dL, odds ratio (95% CI)	Moderate hyperglycemia, BG 161–200 mg/dL, odds ratio (95% CI)	Severe hyperglycemia, BG >200 mg/dL, odds ratio (95% CI)
Operative day					
Death	1.17 (0.15–9.15)	1.0	0.96 (0.65–1.40)	1.11 (0.72–1.72)	1.24 (0.77–2.00)
Cardiac arrest		1.0	1.04 (0.56–1.94)	1.34 (0.68 – 2.67)	1.13 (0.52–2.46)
Myocardial infarction	1.23 (0.61–2.47)	1.0	1.55 (0.73–3.32)	1.69 (0.74–3.88)	1.69 (0.74–3.88)
Surgical site infection	0.68 (0.16–2.92)	1.0	1.21 (0.97–1.52)	1.44 (1.10–1.87)*	1.00 (0.73–1.36)
Respiratory complications	1.75 (0.49–6.23)	1.0	1.30 (0.99–1.72)	1.37 (1.00–1.89)†	1.55 (1.10–2.18)†
Operative reintervention	1.76 (0.65–4.78)	1.0	1.07 (0.85–1.35)	1.00 (0.76–1.33)	1.37 (1.02–1.83)†
Urinary tract infection	0.82 (0.11–6.24)	1.0	0.98 (0.70–1.37)	1.06 (0.72 – 1.57)	1.42 (0.95–2.13)
Venous thromboembolism		1.0	1.11 (0.55–2.23)	1.64 (0.77–3.48)	1.88 (0.84–4.21)
Postoperative day 1					
Death	2.20 (0.88–5.44)	1.0	1.04 (0.71–1.52)	1.30 (0.81–2.09)	1.97 (1.23–3.15)*
Cardiac arrest	2.79 (0.61–12.68)	1.0	0.95 (0.50–1.82)	1.70 (0.81–3.55)	2.31 (1.08–4.98)*
Myocardial infarction	6.74 (1.75–25.97)*	1.0	2.20 (1.05–4.60)†	3.44 (1.51–7.84)*	3.94 (1.64–9.58)*
Surgical site infection	1.38 (0.73–2.62)	1.0	0.91 (0.73–1.14)	0.93 (0.68 – 1.27)	0.91 (0.65–1.29)
Respiratory complications	1.51 (0.73–3.12)	1.0	1.19 (0.93–1.53)	1.23 (0.88–1.71)	1.35 (0.95–1.93)
Operative reintervention	2.46 (1.40–4.35)*	1.0	1.08 (0.86–1.35)	1.20 (0.89–1.63)	1.37 (0.97–1.93)
Urinary tract infection	1.53 (0.59–3.97)	1.0	1.32 (0.95–1.84)	1.67 (1.11–2.51)†	1.68 (1.08–2.63)†
Venous thromboembolism	1.08 (0.12–9.77)	1.0	1.47 (0.72–2.99)	1.03 (0.37–2.85)	2.78 (1.18–6.56)†

BG, blood glucose.
*$p \leq 0.01$.
†$p \leq 0.05$.

demonstrated that strict glycemic control reduced mortality in SICU patients but not in MICU patients, suggesting that this approach might be beneficial in surgical critically ill patients.[22]

Optimism about the effects of strict glycemic control in critically ill surgical patients has led to interest in the effect of glycemic control on surgical outcomes outside of the ICU. Cardiac surgery has received the most attention, and various studies have identified perioperative hyperglycemia as a risk factor for mortality,[10-12] sternal wound infection,[10] prolonged mechanical ventilation,[10] and prolonged hospital stay[10,14] after cardiac surgery. Although much of the literature in general surgery has focused on hyperglycemia and postoperative infections,[1,5,16,23-25] the present study identified MI as the outcome most strongly associated with hyperglycemia after colectomy. A few studies have similarly documented increased risk of MI in hyperglycemic patients after noncardiac surgery[4] and carotid endarterectomy.[26]

Perioperative acute stress-induced hyperglycemia can lead to increased risk of MI both by augmenting cardiac left ventricular strain and promoting a prothrombotic state. Hyperglycemia induces a state of oxidative stress[27,28] characterized by decreased endothelial nitric oxide release and subsequent increase in arterial resistance.[29-32] Arterial tree resistance augments systolic blood pressure, ultimately increasing left ventricular workload and myocardial oxygen demand.[33] Hyperglycemia-induced oxidative stress also directly affects the myocardium, leading to disordered calcium signaling and cardiac contractile dysfunction.[34] Additionally, hyperglycemia-induced nitric oxide depletion interferes with endothelial anti-thrombotic function, and hyperglycemia directly promotes thrombotic events by enhancing coagulation factor synthesis[35] and accelerating shear stress–induced platelet activation.[36]

In the present study, even mild hyperglycemia on POD1 was associated with a 2-fold increase in risk of MI, with incremental elevations in risk for each rise in BG level. This suggests that maintaining a perioperative BG of 80 to 120 mg/dL can reduce cardiovascular risk after colectomy. However, hypoglycemia was also associated with elevated risk of MI, emphasizing the importance of avoiding iatrogenic hypoglycemia when targeting a BG of 80 to 120 mg/dL. The increased risk of cardiac arrest and death in patients with severe hyperglycemia on POD1 was probably attributable primarily to increased incidence of MI in these patients.

Like several previous studies,[1,5,16,23-25] the present study

Table 5. Adjusted Risk of Primary Outcomes by Postoperative Day 1 Blood Glucose Category, Showing All Variables Selected (Using Stepwise Regression) for Final Model Inclusion

	Death	MI	Cardiac arrest
Blood glucose category*			
Hypoglycemic	2.19 (0.88−5.44)	6.74 (1.75−25.97)†	2.77 (0.62−12.56)
Normoglycemic	Reference	Reference	Reference
Mildly hyperglycemic	1.04 (0.72−1.52)	2.20 (1.05−4.60)‡	0.95 (0.50−1.82)
Moderately hyperglycemic	1.30 (0.81−2.09)	3.44 (1.51−7.84)†	1.77 (0.85−3.69)
Severely hyperglycemic	1.97 (1.23−3.15)†	3.94 (1.64−9.48)†	2.45 (1.14−5.25)‡
Age, 5-y increase	1.24 (1.13−1.35)§	1.32 (1.13−1.55)§	1.43 (1.21−1.69)§
Black race		0.26 (0.10−0.70)†	
Current smoking		1.80 (1.00 – 3.28)	
Ethanol abuse	1.88 (1.21−2.91)†		1.97 (0.94−4.14)
ASA class			
1−2	Reference	Reference	
3	1.72 (0.98−3.01)	—	
4−5	2.79 (1.48−5.26)†	1.71 (0.97−2.99)	
Preoperative creatinine, increase by 1 mg/dL		1.27 (1.00−1.61)‡	
Preoperative hematocrit, increase by 5%	0.85 (0.74−0.98)*		
Preoperative platelets, increase by 50,000/mL	0.88 (0.82−0.96)†		0.89 (0.77−1.02)
Preoperative WBC,‡ increase by 1,000 cells/mL	1.05 (1.02−1.08)†	1.05 (1.01−1.09)‡	
Cancer location			
Cecal	0.60 (0.36−1.00)		—
Sigmoid colon	0.57 (0.38−0.86)†		0.31 (0.13−0.72)†
Stoma creation	1.51 (1.03−2.21)‡		
Previous stroke, with neurologic deficit		2.71 (1.36−5.41)†	
Diabetes, treated with insulin		2.01 (1.04−3.90)*	
COPD‡		2.26 (1.33−3.84)†	1.89 (1.09−3.28)‡
Dyspnea with minimal exertion	1.35 (0.95−1.91)		
Dyspnea at rest	4.26 (2.11−8.61)§		
Partially dependent functional status			2.52 (1.35−4.70)†
Completely dependent functional status			7.24 (2.57−20.37)§
Dialysis requirement			5.61 (1.35−23.28)‡
Preoperative weight loss	2.00 (1.39−2.88)§		
Disseminated cancer	2.31 (1.53−3.46)§	0.30 (0.09−1.05)	
Congestive heart failure	2.24 (1.30−3.87)†	2.40 (1.08−5.31)†	3.05 (1.42−6.56)†
Ascites	4.65 (2.33−9.30)§	3.90 (1.03−14.81)‡	
Bleeding disorder	0.43 (0.19−0.94)‡		

Surgical site infection was not significantly associated with blood glucose level and is not shown. Operative day blood glucose category is not shown because there were few associations with study outcomes.

ASA, American Society of Anesthesiologists; WBC, white blood cells.

*Hypoglycemia: blood glucose (BG) <80 mg/dL; normoglycemia: BG 80−120 mg/dL; mild hyperglycemia, BG 121−160 mg/dL; moderate hyperglycemia, BG 161−200 mg/dL; severe hyperglycemia, BG >200 mg/dL.

†$p \leq 0.01$.

‡$p \leq 0.05$.

§$p \leq 0.001$.

also identified a relationship between perioperative hyperglycemia and postoperative infection (eg, UTI; respiratory complications, which included pneumonia; and SSI). Acute perioperative hyperglycemia can increase the risk of infection through similar pathways to those implicated in chronically hyperglycemic diabetic patients: impairing polymorphonuclear leukocyte chemotaxis, bactericidal action, phagocytosis, and T-cell function.[37-40]

Finally, the present study identified an association between severe hyperglycemia and increased risk of operative reintervention and VTE. Increased need for operative reintervention might stem from the higher incidence of SSI

(requiring surgical wound debridement or abscess drainage) and respiratory complications (requiring tracheostomy) in hyperglycemic patients. The association between hyperglycemia and VTE might be a result of the induction of a hypercoagulable state, as discussed here.

Although this study examined glucose levels and not glycemic control protocols, a number of studies have aimed to identify protocols to achieve perioperative strict glycemic control and minimize iatrogenic hypoglycemia. Perhaps the most intriguing strategy is use of the closed-loop artificial endocrine pancreas system. The artificial pancreas continuously monitors BG and administers insulin, glucose, or glucagon as needed to achieve glycemic control within a prescribed target range. In theory, the artificial pancreas should reduce nursing workload and decrease the incidence of hypoglycemia and improve glycemic control.[41] In small randomized clinical trials comparing the artificial pancreas to sliding-scale insulin administration, the artificial pancreas was associated with improved glycemic control after both hepatic[42] and pancreatic[43] resection. After hepatic resection, use of the artificial pancreas was also associated with decreased incidence of SSI and shortened hospital length of stay, compared with sliding-scale insulin administration.[42] In both studies, no patient in either arm experienced hypoglycemia (BG <40 mg/dL), although the studies were small (n = 88, hepatic resection; n = 32, pancreatic resection).[42,43]

The major strength of this study was use of the linked VASQIP−Decision Support Services database, which provided a large representative sample of the US Veteran population. Patient data in the VASQIP, including predefined surgical outcomes, are prospectively collected, helping to minimize reporting bias. There are some study limitations due to the retrospective analysis of such a database. Lack of randomization complicates assessment of cause and effect in a retrospective study. Although hyperglycemia might have been causally related to adverse outcomes after colectomy, hyperglycemia can also serve as a marker for a stress response to such complications. Additionally, information was not available about BG-lowering regimens. Some patients were doubtless normoglycemic due to lack of a stress-induced hyperglycemic response, and others were normoglycemic due to therapeutic glycemic control. In addition, hemoglobin A1c values were not available for the majority of patients and were not analyzed. However, the influence of hemoglobin A1c on colectomy outcomes is unknown, making its relevance to this study unclear.

CONCLUSIONS

We have demonstrated that, in a large cohort of US Veterans, perioperative hyperglycemia was independently related to adverse outcomes, including death, after colectomy for cancer. Any level of hyperglycemia, including mild hyperglycemia (BG 121 to 160 mg/dL), was associated with a ≥2-fold increase in the risk of postoperative MI. Although this does not prove causation, it does indicate that no level of hyperglycemia is safe after cancer colectomy. This suggests that maintaining BG between 80 and 120 mg/dL could reduce the risk of adverse outcomes, especially perioperative MI, although care should be taken to avoid iatrogenic hypoglycemia, which was also associated with adverse outcomes after colectomy for cancer. We also demonstrated that perioperative normoglycemia was not achieved in the majority of both diabetic and nondiabetic patients. If future prospective studies indicate that maintaining a BG of 80 to 120 mg/dL is beneficial, substantial improvements in outcomes after cancer colectomy can be realized through implementation of strict glycemic control.

Appendix: CPT codes used to define open colectomy for cancer

CPT	Description
44140	Colectomy, partial; with anastamosis
44141	Colectomy, partial; with skin-level cecostomy or colostomy
44143	Colectomy, partial; with end colostomy and closure of distal segment (Hartmann type procedure)
44144	Colectomy, partial; with resection, with colostomy or ileostomy and creation of mucofistula
44145	Colectomy, partial; with coloproctostomy (low pelvic anastamosis)
44146	Colectomy, partial; with coloproctostomy (low pelvic anastamosis), with colostomy
44150	Colectomy, total, abdominal, without proctectomy; with ileostomy or ileoproctostomy
44151	Colectomy, total, abdominal, without proctectomy; with continent ileostomy

Author Contributions

Study conception and design: Jackson, Macsata, Amdur
Acquisition of data: Amdur, Macsata
Analysis and interpretation of data: Jackson, Amdur
Drafting of manuscript: Jackson
Critical revision: White, Macsata, Amdur

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