The Clinical Significance of an Elevated Postoperative Glucose Value in Nondiabetic Patients after Colorectal Surgery

Evidence for the Need for Tight Glucose Control?

Ravi P. Kiran, MBBS, MS, FRCS, FACS, MSc, Matthias Turina, MD, PhD, Jeff Hammel, MS, and Victor Fazio, MB, MS, MD (Hon), FRACS, FRACS (Hon), FACS, FRCS

Objectives: To evaluate the significance of hyperglycemia in patients without a preoperative diagnosis of diabetes undergoing elective colorectal surgery.
Methods: Preoperative and all postoperative blood glucose measurements were retrieved for 2628 consecutive patients undergoing elective colorectal resection within 2 years at 1 center. Nondiabetic patients were identified as those without a preoperative diagnosis of diabetes and/or based on HbA_{1C} levels. The association between any elevated postoperative random glucose value (hyperglycemia: >125 mg/dL) and level of elevation (>125 mg/dL or >200 mg/dL) within 72 hours of surgery in nondiabetic patients with 30-day mortality and infectious and noninfectious complications was assessed.
Results: Evaluation of 16,404 postoperative glucose measurements for all 2447 nondiabetic patients who underwent surgery in 2010 and 2011 revealed that 66.7% patients experienced hyperglycemia. Degree of hyperglycemia correlated with increasing American Society of Anesthesiologists class and surgical severity (blood loss). Hyperglycemia was associated with infectious and noninfectious complications and mortality, the rates of these complications increasing parallel to the degree of hyperglycemia. Hyperglycemia was independently associated with septic complications ($P = 0.024$).
Conclusions: Postoperative hyperglycemia is frequent after elective colorectal surgery in nondiabetic patients. Even a single postoperative elevated glucose value is adversely associated with morbidity and mortality; this risk is related to the degree of glucose elevation. These findings strongly support monitoring of glucose values and early consideration of management strategies for glycemic control after surgery even in nondiabetic patients.

Keywords: colon, complication, glucose, hyperglycemia, laparoscopy, rectal, resection, surgery

(*Ann Surg* 2013;258:599–605)

Although uncontrolled perioperative hyperglycemia is a risk factor for adverse outcome in both diabetic and nondiabetic patients after trauma and cardiovascular surgery, its risks in elective abdominal surgery are less well-defined. After major surgery and trauma, perioperative blood glucose elevations may be associated with previously undiagnosed diabetes mellitus or occur because of the activation of the hypothalamic-pituitary axis as a physical response to severe stress in individuals at risk. A number of recent studies[1–6] have demonstrated that uncontrolled perioperative hyperglycemia may be associated with increased surgical site infections (SSIs) in both diabetic and nondiabetic patients undergoing general and colorectal surgical procedures. However, existing studies are disadvantaged by the inclusion of diverse patient subgroups with variable disease processes, illness severity, and operative complexity, which renders their ability to evaluate the specific role of hyperglycemia on any detected differences in outcomes difficult. The true risk and significance of perioperative hyperglycemia in nondiabetic individuals undergoing elective colorectal surgery, therefore, remains largely unclear and presents the basis for this study. Bacterial contamination commonly occurs in colorectal operations and leads to rates of SSIs and septic infections that typically exceed those of other abdominal operations.[7] Furthermore, considering that colorectal surgery involves patients and conditions of varying complexity and operations of differing severity and duration that could provoke a significant stress response, this provides an ideal cohort for the evaluation of the influence of hyperglycemia on outcomes after surgery.

The aim of this study was to evaluate whether perioperative hyperglycemia is associated with higher rates of SSI, organ failure, and mortality in a large uniform cohort of nondiabetic colorectal surgery patients. It is our hypothesis that perioperative hyperglycemia is associated with a higher incidence of septic complications and subsequent organ failure irrespective of previous diabetic status.

METHODS

Study Design and Patient Population

All patients undergoing abdominal colorectal surgery operations at a single-center teaching hospital between January 1, 2010 and December 31, 2011 were identified from an institutional review board–approved database. Data for these patients were obtained from the database and from additional chart review, as required. Diabetic patients on admission were identified as outlined later and separated out from previously nondiabetic patients. Patients were then grouped according to their highest blood glucose value in the first 48 postoperative hours into the subgroups "normoglycemia," "mild hyperglycemia," and "severe hyperglycemia" as defined later.

Inclusion/Exclusion Criteria

All adult patients (18 years of age or older) undergoing any open or laparoscopic colon or rectal resection were included for analysis. Indications were grouped into inflammatory bowel disease, neoplasms (adenoma and cancer), and others (diverticulitis, prolapse, etc). Patients undergoing small bowel resections were excluded except those who underwent an ileoanal J-pouch procedure. Patients who underwent exploratory laparotomy for small bowel or colorectal pathology but did not undergo colonic or rectal resection were excluded. Patients who underwent transanal or isolated pelvic resection (Altemeier, Delorme, etc) were also excluded.

Parameters of Interest

Demographic and perioperative parameters included age, indication for surgery, American Society of Anesthesiologists (ASA)

From the Department of Colorectal Surgery, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH.
Disclosure: The authors declare no conflicts of interest.
Reprints: Ravi P. Kiran, MBBS, MS, FRCS, Division of Colorectal Surgery, Columbia University Medical Center/New York Presbyterian Hospital, Floor 8, Herbert Irving Pavilion, New York, NY 10021. E-mail: rpk2118@columbia.edu

ISSN: 0003-4932/13/25804-0599
DOI: 10.1097/SLA.0b013e3182a501e3

status, and body mass index. Perioperative parameters included operative time (from skin incision to skin closure), estimated blood loss, intraoperative complications, and transfusion requirements. Postoperative variables of interest were anastomotic leaks, cardiovascular complications (myocardial infarction and arrhythmia), deep venous thrombosis, length of hospital stay (LOS), readmission, reoperation, reintubation, and overall mortality. Superficial, deep, and organ/space SSIs; pneumonia; and urinary tract infections were considered infectious complications. Sepsis was defined as the presence of any infectious focus in combination with positive blood cultures or polymerase chain reaction and 2 or more positive criteria for systemic inflammatory response syndrome as defined by the American College of Chest Physicians and the Society of Critical Care Medicine.[8]

Definition of Hyperglycemia and Diabetes Mellitus

Because patients are usually fasting at the time of surgery, those with an initial postoperative glucose value of 125 mg/dL or less were defined "normoglycemic," whereas those with glucose values of more than 125 mg/dL were defined "hyperglycemic" for the purpose of this study. Hyperglycemia was further divided into "mild hyperglycemia" (blood glucose values of 125–199 mg/dL) and "severe hyperglycemia," defined as random blood glucose values of 200 mg/dL or greater. All blood glucose measurements derived from venous blood samples, arterial blood gas analyses, or finger-stick glucose measurements from admission to 48 hours postoperatively were included (minimum 3 measurements), whereas hyperglycemia occurring later than 48 hours postoperatively was not included in this analysis. Preexisting diabetes mellitus was defined as the presence of a known diagnosis of diabetes mellitus or of HbA_{1C} levels of 6.5% or more on admission, when these were known (Fig. 1). Admission random or fasting blood glucose values were not used to identify patients with preexisting diabetes.

Statistical Analysis

Statistical analyses were performed using descriptive statistics for demographic data. For groupwise comparisons, Student *t* test (normal distribution) or Mann-Whitney *U* test for nonparametric distributions of data were used. For comparisons of more than 2 groups, analysis of variance (normal distribution) or the Kruskal-Wallis test for nonnormally distributed parameters was applied. To compare nominal data, the χ^2 test or the Fisher exact test was used. A stepwise forward logistic regression model was applied for multivariate analysis to detect independent predictors of septic infections and organ failure.

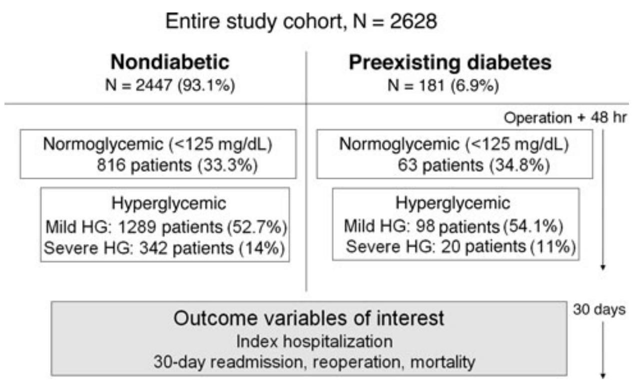

FIGURE 1. An overview of the study cohort with respect to diabetes status and level of glycemia. Note that glucose levels included in this study had to be obtained during the first 48 postoperative hours, but outcome variables pertain to 30 postoperative days. HG indicates hyperglycemia.

RESULTS

An overview of the patient population is provided in Table 1. A total of 2628 patients met the inclusion criteria and were included in the analysis and 181 (6.9%) patients were diagnosed with preexisting diabetes mellitus by the criteria listed previously. A total of 2447 (93.1%) patients were nondiabetic, had a total of 16,404 glucose measurements, which revealed that 66.7% of these patients experienced postoperative hyperglycemia of more than 125 mg/dL. Hyperglycemia was observed more frequently among patients undergoing resection for colorectal neoplasms as opposed to other indications (Table 1). Patients who developed hyperglycemia were also more likely to have higher ASA class than those with normoglycemia. Only 1 patient in the entire study cohort developed postoperative hypoglycemia of less than 50 mg/dL and 3 patients had values between 50 and 70 mg/dL.

Hyperglycemia and Outcomes in Nondiabetic Patients

An analysis of the common outcome variables by level of postoperative glycemia in nondiabetic patients is provided in Table 2. Univariate associations were found between postoperative hyperglycemia and the length of operation, extent of blood loss, and transfusion requirements. Hyperglycemia (mild or severe) was associated with increased rates of infectious complications (superficial and deep SSI, urinary tract infections), sepsis, acute renal failure, reintubation and a greater LOS. The risk for complications increased with an increasing level of postoperative glycemia. The frequency of postoperative sepsis was 0.61% in patients with normoglycemia and 3.5% in patients with any blood glucose level of more than 200 mg/dL during the first 48 postoperative hours. Similarly, reoperations were twice as frequent for patients with severe hyperglycemia when compared with those with normoglycemia (7.3% vs 3.1%, $P = 0.006$). Although rare, postoperative mortality was significantly associated with postoperative glycemia, with only 1 (0.12%) patient with normoglycemia having died during the first 30 postoperative days as compared with 4 (1.2%) of the patients who had 1 or more values of severe postoperative hyperglycemia.

Effect of Postoperative Hyperglycemia on Nondiabetic Patients When Compared With Diabetic Patients

A comparison of the chosen outcome variables for diabetic and nondiabetic patients with postoperative hyperglycemia is shown in Table 3. Of note, none of the examined outcome parameters differed between diabetic and nondiabetic patients.

Association of Postoperative Hyperglycemia With Specific Outcomes in Nondiabetic Patients

Significant univariate associations (listed in Table 2) were entered into a linear regression model to identify independent predictors for such specific complications as sepsis, renal failure, reoperation, and LOS (Tables 4 and 5). The analysis suggested that sepsis was associated with ASA score of 3 or more ($P = 0.014$) and postoperative hyperglycemia ($P = 0.025$) (Table 4). Renal failure (Table 4) was independently associated with ASA score of 3 or more ($P = 0.03$) and emergency surgery ($P = 0.03$),but not the presence of postoperative hyperglycemia ($P = 0.45$). Reoperation and LOS were, however, independently associated with hyperglycemia (Table 5). Nondiabetic patients with mild hyperglycemic had a 17% and those

TABLE 1. Characteristics of the Patients (Diabetic and Nondiabetic)

	Level of Glycemia (mg/dL)				
	Overall	Normoglycemic (≤125)	Mild HG (126–200)	Severe HG (>200)	*P*
No. patients	N = 2628	879 (33.4%)	1387 (52.8%)	362 (13.8%)	
Age (yr)	50.0 ± 17.3	49.0 ± 17.2	50.4 ± 17.3	50.7 ± 17.4	0.08
BMI (kg/m^2)	26.5 ± 6.3	26.5 ± 6.2	26.4 ± 6.2	26.8 ± 6.7	0.87
Diabetes mellitus (%)	181 (6.9%)	63 (7.2%)	98 (7.1%)	20 (5.5%)	0.63
Preoperative steroid use	50 (1.9%)	17 (1.9%)	30 (2.2%)	3 (0.8%)	0.25
ASA 1: Mild disturb	1312 (50.8%)	498 (58.0%)	720 (52.6%)	94 (26.6%)	**<0.001**
ASA 3: Severe disturb	1128 (43.7%)	319 (37.1%)	587 (42.8%)	222 (62.9%)	
Emergency operation	61 (2.4%)	11 (1.3%)	38 (2.8%)	12 (3.4%)	0.1
Indication for surgery					
IBD	855 (32.5%)	308 (35%)	461 (33.2%)	86 (23.8%)	**<0.001**
Neoplasm	693 (26.4%)	172 (19.6%)	386 (27.8%)	135 (37.3%)	
Diverticulitis	220 (8.4%)	59 (6.7%)	132 (9.5%)	29 (8.0%)	
Other	860 (32.7%)	340 (38.7)	408 (29.5%)	112 (30.9%)	

Data presented as mean ± SD and as % Demographic parameters and indication for surgery in the entire study population including diabetic and nondiabetic patients by level of glycemia.

BMI indicates body mass index; HG, hyperglycemia; IBD, inflammatory bowel disease (combining ulcerative colitis and Crohn's disease).

TABLE 2. Outcome Variables for Nondiabetic Patients

	Level of Glycemia (mg/dL)				
	Overall	Normoglycemic (≤125)	Mild HG (126–200)	Severe HG (>200)	*P*
Intraoperative					
No. patients	2447	816 (33.3%)	1289 (52.7%)	342 (14.0%)	
EBL	166 ± 187	129 ± 130	185 ± 198	212 ± 282	**<0.001***
Transfusion (no. patients)	234 (9.6%)	39 (4.8%)	133 (10.3%)	62 (18.1%)	**<0.001***
Length of surgery (min)	158.2 ± 96.1	136.7 ± 88.4	166.4 ± 96.3	180.7 ± 104.0	**<0.001***
Diverting ostomy	21.9%	16.2%	24.6%	24.3%	**0.006***
Postoperative					
Acute renal failure	34 (1.4%)	4 (0.49%)	18 (1.4%)	12 (3.5%)	**0.001†**
Anastomotic leak	60 (2.5%)	12 (1.5%)	39 (3.0%)	9 (2.6%)	0.03‡
Arrhythmia	46 (1.9%)	7 (0.86%)	24 (1.9%)	15 (4.4%)	**<0.001†**
Myocardial infarction	5 (0.20%)	0 (0%)	3 (0.23%)	2 (0.58%)	0.07
Pneumonia	22 (0.90%)	5 (0.61%)	10 (0.78%)	7 (2.0%)	0.07
Reintubation	9 (0.37%)	1 (0.12%)	3 (0.23%)	5 (1.5%)	**0.006†**
Sepsis	45 (1.8%)	5 (0.61%)	28 (2.2%)	12 (3.5%)	**0.002***
SSI deep	12 (0.49%)	4 (0.49%)	3 (0.23%)	5 (1.5%)	**0.026†**
SSI superficial	107 (4.4%)	24 (2.9%)	62 (4.8%)	21 (6.1%)	**0.028***
SSI organ/space	96 (3.9%)	24 (2.9%)	56 (4.3%)	16 (4.7%)	0.2
UTI	95 (3.9%)	25 (3.1%)	49 (3.8%)	21 (6.1%)	**0.046†**
DVT	65 (2.7%)	10 (1.2%)	37 (2.9%)	18 (5.3%)	**<0.001***
Length of stay (d)	8.2 ± 7.1	6.80 ± 5.6	8.4 ± 6.45	11.1 ± 10.8	**<0.001***
Readmission	295 (12.1%)	88 (10.8%)	165 (12.8%)	42 (12.3%)	0.38
Reoperation	114 (4.7%)	25 (3.1%)	64 (5.0%)	25 (7.3%)	**0.006***
Mortality	9 (0.37%)	1 (0.12%)	4 (0.31%)	4 (1.2%)	**0.042†**

Outcome variables stratified by level of glycemia. *P* values indicate probabilities of significant differences found by analysis of variance testing, and footnote symbols (*, †, or ‡) indicate the group(s) that differ from normoglycemia as reference.

*Indicates significant difference between normoglycemia and mild or severe hyperglycemia.

†Indicates significant difference between normoglycemia and severe hyperglycemia.

‡Indicates significant difference between normoglycemia and mild hyperglycemia.

DVT indicates deep venous thrombosis; EBL, estimated blood loss; HG, hyperglycemia; UTI, urinary tract infection.

with severe hyperglycemia had a 28% estimated greater median LOS than patients with normoglycemia.

DISCUSSION

Perioperative hyperglycemia has been linked to adverse outcome in several subgroups of surgical patients, even before van den Berghe's landmark trial on the benefits of tight glucose control in decreasing mortality in nondiabetic critically ill surgical intensive care unit patients sparked an intense debate about glucose control in such patients.[9] A higher incidence of SSIs in cardiac surgery patients[10–12] (notably sternal wound infections), or a longer intensive care unit and hospital stay, a higher rate of pneumonia, and increased mortality in trauma patients[13,14] have been reported in patients with perioperative hyperglycemia. However, the risk of uncontrolled or poorly controlled hyperglycemia in previously nondiabetic patients undergoing elective noncardiovascular surgery remains poorly understood. The purpose

TABLE 3. Postoperative Outcomes for Nondiabetic and Diabetic Patients With Any Degree (Mild or Severe) of Postoperative Hyperglycemia

	Nondiabetic	Diabetic	P
No. patients	1631 (93.1%)	118 (6.9%)	
Acute renal failure	30 (1.8%)	1 (0.85%)	0.72
Anastomotic leak	48 (2.9%)	5 (4.2%)	0.4
Arrhythmia	39 (2.4%)	3 (2.5%)	0.76
Myocardial infarction	5 (0.31%)	1 (0.85%)	0.34
Pneumonia	17 (1.0%)	1 (0.85%)	>0.99
Reintubation	8 (0.49%)	0 (0%)	1
Sepsis	40 (2.5%)	2 (1.7%)	1
SSI deep	8 (0.49%)	0 (0%)	1
SSI superficial	83 (5.1%)	4 (3.4%)	0.42
SSI organ/space	72 (4.4%)	9 (7.6%)	0.11
UTI	70 (4.3%)	6 (5.1%)	0.68
DVT	55 (3.4%)	3 (2.5%)	0.79
Length of stay (d)	9.0 ± 7.6	9.01 ± 6.6	0.44
Readmission	207 (12.7%)	13 (11.0%)	0.6
Reoperation	89 (5.5%)	6 (5.1%)	0.86
Mortality	8 (0.49%)	0 (0%)	1

Univariate groupwise comparison between diabetic and nondiabetic patients regardless of level of glycemia.

DVT indicates deep venous thrombosis; UTI, urinary tract infection.

TABLE 4. Independent Risk Factors Associated With Sepsis and Renal Failure in Nondiabetic Patients

Characteristic	OR	95% CI	P
Sepsis			
Steroid use	1.61	0.20–12.9	0.66
Age <50 yr	2.50	0.94–6.66	0.07
ASA score ≥3	4.14	1.33–12.9	**0.014**
Emergency surgery	2.54	0.53–12.2	0.24
Surgery time ≥180 min	1.15	0.45–2.91	0.78
Hyperglycemia group			Overall **0.025**
Normoglycemia (reference)	1.0		
Mild hyperglycemia	7.85	1.02–60.5	**0.048**
Severe hyperglycemia	8.03	0.91–71.3	**0.06**
Renal failure			
Steroid use	5.04	0.56–45.4	0.15
Age <50 yr	1.18	0.34–4.06	0.79
ASA score ≥3	9.72	1.20–79.0	**0.03**
Emergency surgery	6.34	1.20–33.5	**0.03**
Surgery time ≥180 min	1.64	0.47–5.77	0.44
Hyperglycemia group			Overall 0.45
Normoglycemia (reference)	1.0		
Mild hyperglycemia	1.05	0.20–5.66	0.95
Severe hyperglycemia	2.46	0.42–14.4	0.32

Independent risk factors for sepsis and renal failure identified by stepwise forward logistic regression analysis.

ASA indicates American Society of Anesthesiologists; CI, confidence interval; OR, odds ratio.

TABLE 5. Independent Risk Factors Associated With Reoperation and Length of Hospital Stay in Nondiabetic Patients

Characteristic	OR	95% CI	P*
Reoperation			
Steroid use	2.29	0.66–7.93	0.19
Age <50 yr	0.70	0.41–1.18	0.18
ASA ≥3	0.62	0.36–1.09	0.09
Emergency surgery	3.80	1.48–9.76	**0.005**
Surgery time ≥180 min	1.26	0.74–2.16	0.40
Hyperglycemia group			Overall 0.007
Normoglycemia (reference)	1.0		
Mild hyperglycemia	2.10	1.05–4.20	**0.036**
Severe hyperglycemia	3.83	1.63–9.01	**0.002**
Characteristic	**Medians Ratio***	**95% CI**	**P†**
Length of stay			
Steroid use	1.03	0.83–1.28	0.77
Age <50 yr	0.95	0.89–1.02	0.15
ASA score ≥3	1.21	1.13–1.30	**<0.001**
Emergency surgery	1.53	1.26–1.86	**<0.001**
Surgery time ≥180 min	1.30	1.21–1.40	**<0.001**
Hyperglycemia Group			Overall <0.001
Normoglycemia (reference)	1.0		
Mild hyperglycemia	1.16	1.08–1.26	**<0.001**
Severe hyperglycemia	1.28	1.14–1.43	**<0.001**

Independent risk factors for reoperation and increased length of hospital stay identified by stepwise forward logistic regression analysis.

*The modeled outcome was $\log_2$ (LOS), yielding an estimate of the relative increase in median LOS corresponding to the characteristic. We call this the "medians ratio."

†Multivariable P values, adjusting for the other preselected model covariates.

ASA indicates American Society of Anesthesiologists; CI, confidence interval; OR, odds ratio.

of this study was to specifically determine the association of perioperative hyperglycemia with outcomes for patients undergoing major colorectal surgery. Only patients who underwent colon or rectal resection were selected to minimize differences in the extent of surgery that may impact any detected outcomes between groups. Because an established preoperative diagnosis of diabetes mellitus triggers greater attention to the monitoring and control of glucose, patients with a history of diabetes or a measured HbA_{1C} level indicating diabetes were excluded.

Prior studies have shown a high incidence of perioperative hyperglycemia in general surgery patients.[1,2] We similarly found that postoperative hyperglycemia occurred in the majority of nondiabetic in addition to known diabetic patients undergoing colorectal surgery. In fact, only 1 of 3 patients did not have an elevated glucose value, that is, remained normoglycemic during the first 48 postoperative hours, which mirrors the incidence of hyperglycemia found in a large recent study on general surgery patients by Kwon et al.[1] The distribution of postoperative blood glucose values in our cohort was in fact almost identical in diabetic compared with nondiabetic patients. Although it may be argued that blood glucose control in known diabetic patients may have been inadequate with only 34% of diabetic patients remaining normoglycemic, it may equally be concluded that perioperative insulin therapy succeeded in establishing their glucose control to a similar pattern and level as nondiabetic patients, thus lowering the incidence of hyperglycemia-related complications to that seen in nondiabetic controls. Regardless of the cause and effect associations, the additional finding that the occurrence of various complications was similar for patients with and without a known preoperative diagnosis of diabetes who developed hyperglycemia supports the need for monitoring of and attention to postoperative glucose values even in nondiabetic patients after colorectal surgery. Our finding that the frequency of several complications increased with the degree of hyperglycemia in nondiabetic patients further supports this contention.

The association between perioperative hyperglycemia and infectious complications in colorectal surgery patients has previously been variably reported. Ata et al[3] showed that postoperative hyperglycemia greater than 140 mg/dL was the strongest independent predictor of SSI on multivariate analysis of a subgroup of 226 colorectal surgery patients. Serra-Aracil X et al[6] in their prospective observational study on 611 patients with colorectal cancer resections published in 2011 found that hyperglycemia greater than 200 mg/dL at 48 hours postoperatively was associated with an increased risk of organ/space SSI after rectal cancer resections but not so after resections of colonic cancers. On the contrary, Vanessa Ho et al[4] published a comprehensive analysis of patient- and treatment-related factors associated with SSI in 650 colorectal surgery patients and reported that even a single postoperative glucose measurement above 200 mg/dL during the first 7 postoperative days was predictive of subsequent organ/space SSIs but not so of incisional SSIs. Finally, a large recent study by Kwon et al,[1] examining postoperative glucose values of 11,633 patients undergoing colorectal or bariatric operations from the Surgical Care Outcomes and Assessment Program, found that patients with hyperglycemia had a significantly increased risk of infection (odds ratio: 2.0), reoperation (odds ratio: 1.8), and mortality (odds ratio: 2.7). The authors of this study used a time window of 48 hours postoperatively and a threshold value of 180 mg/dL in their analysis. Interestingly enough, Kwon et al described a dose-effect relationship between the effectiveness of insulin-related glucose control and adverse outcome, with best results seen in patients with glucose levels less than 130 mg/dL and worst outcome in those with levels persisting greater than 180 mg/dL.

By minimizing the drawbacks of several of these previous studies, the design of our study allows for a better evaluation of the impact of postoperative hyperglycemia on outcomes for nondiabetic patients undergoing colorectal surgery. First, we chose to focus on a uniform patient population at a single center who underwent only abdominal or pelvic surgery that required colorectal resection, thereby minimizing potential bias because of differences in the nature and intensity of the operation, perioperative management, and postoperative course that could contribute to any detected hyperglycemia and postoperative outcomes. Second, we included patients with mild hyperglycemia of 125 to 200 mg/dL, thereby allowing us to study this important, large group of patients that was previously considered unproblematic, especially if no previous diagnosis of diabetes mellitus was made. Our findings in this group of patients with only mild hyperglycemia are in line with a recent analysis of 9638 patients undergoing colectomy for cancer from the Veterans Administration Surgical Quality Improvement Program database by Jackson et al,[15] who similarly found that even mild hyperglycemia on postoperative day 1 was associated with a more than 2-fold increased risk for adverse outcomes in nondiabetic patients.

The results of our analysis suggest that postoperative hyperglycemia even in patients deemed to be nondiabetic at the time of surgery is significantly associated with adverse postoperative outcomes. Nondiabetic patients with hyperglycemia had an increased risk of infectious complications, sepsis, postoperative renal failure, and mortality compared with patients who remained normoglycemic during the first 48 hours after surgery. Similarly, the rates of reintubation, reoperation, and LOS for patients who developed hyperglycemia were significantly greater than for normoglycemic controls in the multivariate analysis, which accounted for factors such as age, ASA class, or preoperative steroid use. Despite the ability of our study to counter some of the disadvantages of the previous literature, certain potential shortcomings also need due discussion. By the nature of its retrospective design, no inferences can be made about what came first, postoperative hyperglycemia or the onset of subsequent morbidity, for example, an infectious complication. However, we chose to include only acute glucose elevations during the first 48 postoperative hours, it is hence likely that hyperglycemic events in this time frame precede the onset of infections in previously nondiabetic patients, as also suggested by others.[16] Only sliding-scale insulin was used for the control of elevated glucose for patients in this study, without the use of strict insulin regimens to achieve normoglycemia. Only 1 patient developed hypoglycemia less than 50 mg/dL during this study period. Thus, any presumptions about the potential avoidance of hyperglycemia-related complications by early insulin therapy as also the influence of such therapy on the causation of hypoglycemia or its consequences are also not permissible. Thus, any potential benefits of strict insulin regimens to maintain blood glucose levels in the physiologic range can only be speculated. Notwithstanding the recently published, more conservative guidelines for intensive insulin therapy in hospitalized patients that reflect an increasing concern for iatrogenic hypoglycemia,[17–19] the findings of our study support the routine monitoring of and attention to elevated postoperative blood glucose values even in nondiabetic patients.

The incidence of severe iatrogenic hypoglycemia (≤40 mg/dL) during intensive insulin therapy in critically ill intensive care unit patients was shown to be as high as 6.8% in the NICE SUGAR trial.[20] A post hoc analysis could further show that adjusted hazard ratios for death in patients experiencing moderate (41–70 mg/dL) or severe (≤40 mg/dL) hypoglycemia were 1.4 and 2.1, respectively.[21] Although the patient population studied in the NICE SUGAR trial clearly differs from the average postoperative patient in colorectal surgery, the risks of inadvertent hypoglycemia must also be carefully considered.

Future studies may help elucidate whether the prompt management of any abnormal glucose values promotes outcomes and clarify whether such derangements are a marker for, or instead, contribute to eventual complications. With respect to the definitions of hyperglycemia as used in this study, it may be argued that postoperative glucose levels of 125 mg/dL or less are not necessarily physiologic as patients may no longer be fasting in the 48-hour period after surgery or because hyperglycemia may be iatrogenically induced by dextrose-containing intravenous solutions; medications such as corticosteroids, beta-blockers, or thiazide diuretics; or total parenteral nutrition.[22] To account for such expected minor postoperative blood glucose elevations, we chose to include a wide range of blood glucose values as "mild hyperglycemia" in our analysis. Because fasting blood glucose measurements (value greater than 125 mg/dL: diabetes) were not used to stratify patients as diabetic or nondiabetic, the nondiabetic group may have included some individuals who would otherwise have been diagnosed as diabetic using these criteria. It is common practice to obtain random, rather than fasting, glucose values as part of the preoperative workup of patients undergoing elective surgery. We hence decided to use only random glucose values for a diagnosis of diabetes in this study, because this would allow for an increased generalizability of our study findings to any patient undergoing surgery.

CONCLUSIONS

The findings of this study suggest that postoperative hyperglycemia is frequent in nondiabetic patients undergoing major colorectal surgery. Even a single postoperative elevated glucose value is adversely associated with morbidity and mortality, this risk related to the degree of glucose elevation. These findings strongly support monitoring of glucose values and early consideration of management strategies for glycemic control after surgery even in nondiabetic patients.

REFERENCES

1. Kwon S, Thompson R, Dellinger P, et al. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. *Ann Surg*. 2013;257:8–14.

2. Turina M, Miller FN, Tucker CF, et al. Short-term hyperglycemia in surgical patients and a study of related cellular mechanisms. *Ann Surg*. 2006;243: 845–851.
3. Ata A, Lee J, Bestle SL, et al. Postoperative hyperglycemia and surgical site infection in general surgery patients. *Arch Surg*. 2010;145:858–864.
4. Ho VP, Stein SL, Trencheva K, et al. Differing risk factors for incisional and organ/space surgical site infections following abdominal colorectal surgery. *Dis Colon Rectum*. 2011;54:818–825.
5. McConnell YJ, Johnson PM, Porter GA. Surgical site infections following colorectal surgery in patients with diabetes: association with postoperative hyperglycemia. *J Gastrointest Surg*. 2009;13:508–515.
6. Serra-Aracil X, Garcia-Domingo MI, Pares D, et al. Surgical site infection in elective operations for colorectal cancer after the application of preventive measures. *Arch Surg*. 2011;146:606–612.
7. Manilich E, Vogel JD, Kiran RP, et al. Key factors associated with postoperative complications in patients undergoing colorectal surgery. *Dis Colon Rectum*. 2013;56:64–71.
8. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101:1644–1655.
9. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359–1367.
10. Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care*. 2010;33:1783–1788.
11. Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. *Endocr Pract*. 2004;10(suppl 2):21–33.
12. Kramer R, Groom R, Weldner D, et al. Glycemic control and reduction of deep sternal wound infection rates: a multidisciplinary approach. *Arch Surg*. 2008;143:451–456.
13. Sung J, Bochicchio GV, Joshi M, et al. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. *J Trauma*. 2005;59:80–83.
14. Yendamuri S, Fulda GJ, Tinkoff GH. Admission hyperglycemia as a prognostic indicator in trauma. *J Trauma*. 2003;55:33–38.
15. Jackson RS, Amdur RL, White JC, et al. Hyperglycemia is associated with increased risk of morbidity and mortality after colectomy for cancer. *J Am Coll Surg*. 2012;214:68–80.
16. Bochicchio GV, Bochicchio KM, Joshi M, et al. Acute glucose elevation is highly predictive of infection and outcome in critically injured trauma patients. *Ann Surg*. 2010;252:597–602.
17. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA*. 2008;300:933–944.
18. Mowery NT, Gunter OL, Kauffmann RM, et al. Duration of time on intensive insulin therapy predicts severe hypoglycemia in the surgically critically ill population. *World J Surg*. 2012;36:270–277.
19. Qaseem A, Humphrey LL, Chou R, et al. Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2011;154:260–267.
20. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.
21. Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med*. 2012;367:1108–1118.
22. Rosmarin DK, Wardlaw GM, Mirtallo J. Hyperglycemia associated with high, continuous infusion rates of total parenteral nutrition dextrose. *Nutr Clin Pract*. 1996;11:151–156.

DISCUSSANTS

H.C. Polk (Louisville, KY):

A decade ago, many of us in this room would have probably taken the hypothesis that we could take the elements of the surgical care improvement project, weld them together, get a 95, 90% performance rate, and accomplish a lot of good for our patients. This was certainly the purpose of much of the quality improvement efforts over the last decade.

It turns out that the good things we expected to happen have not uniformly occurred. We have been often disappointed at many things that seemed not to be rocket science should have worked extraordinarily well. It turns out that it has been very difficult to prove that they have been.

This is an important article because it goes back to 1 of the 8 or 10 things in that initial effort, glucose control, and says it really does work in the hands of some people.

I have some questions about this and had the privilege of studying the article. I also have a major conflict of interest in that Dr. Turina did his PhD on these subjects in our laboratory. So, while he has continued to do this, we are certainly biased about some of his thoughts.

First, there are some changes in the article that are not touched in the talk. This is a 2-year study. That at 2000 cases, even for the Cleveland Clinic, is a lot to pack in 1 year. They managed that in 2 years.

The second point in the article is that they do make reference to an issue with tight glucose control that has become very important. Currently, there are several meta-analyses that show that the problem with tight glucose control is that the occasional patient becomes hypoglycemic. That is a real issue. One of the things I would ask the authors is to give their information about how many episodes of hypoglycemia of significant degree occurred in these patients during this time. I am certain the number is not zero.

The nice thing about this study, although, is that the authors are talking about almost a predictive value for this. This is not glucose control out of order after sepsis occurs; it is well before it occurs. I think that is very important.

They have also done a nice job of telling the difference between mild hyperglycemia and severe hyperglycemia and make some useful points about that.

I would also ask Dr. Kiran to address the issue of whether hyperglycemia is really just a surrogate for the really hard case.

All of us remember the forest plot in the *JAMA* article (*JAMA*, August 2008;300(8) 933–944; Fig. 4) that showed that hypoglycemia was to be avoided, but if it occurred, it was catastrophic in reversing the outcome of these efforts. There are more than half a dozen patients, many in the Midwest United States, who have been rendered badly hurt with hypoglycemia and cerebral damage and are working their way through the legal system at this point in time. It is a fine balance. Sometimes perfection is the enemy of good in this effort.

I think there is one other curious business about this that I have not thought about before. A single episode of hyperglycemia, like a single episode of hypothermia, which we are now studying, seems to throw the wheels off the track. A single episode of hypoglycemia seemed to put somebody into this thing. We found the same to be true for hypothermia. A single, brief hypothermic episode disrupts some things. In host defenses, it makes everything very difficult.

Response From R.P. KIRAN:

Thank you, Dr. Polk, for reviewing the article and your comments. Since our study evaluated whether elevated glucose levels after surgery are associated with adverse outcomes, we did not specifically look at the risk of hypoglycemia or its effect were this to occur. Considering the retrospective nature of the study, we were also unable to assess whether the prompt treatment of hyperglycemia, when this occurs, is beneficial to the patients. But I do take your point that any management strategies that include a tight glucose control would need to consider the adverse effects of hypoglycemia.

The second question regarding whether an increased glucose level is a surrogate or a marker for complexity, I think the answer is probably "yes."

The specific question that really needs to be answered in the future is whether even if hyperglycemia represents a marker of a poor physiologic state, severity of operation, or is a harbinger for complication, whether managing this promptly improves outcomes.

There are some data from previous literature that tight glucose control may be associated with better outcomes.

We too found it rather interesting that even a single elevated postoperative glucose was associated with adverse outcomes in our patients. The outcomes in the nondiabetic population closely mirrored those in the diabetic population when hyperglycemia developed. And we do know from previous experience that in diabetic patients it is absolutely paramount to control hyperglycemia. The take-home point from our study is that even in nondiabetic patients undergoing major operations, especially colorectal surgery, the blood glucose needs to be very carefully monitored and managed.

DISCUSSANTS

W.B. Inabnet (New York, NY):

I have 2 short questions.

Despite a well-defined clinical pathway for our diabetic bariatric surgery patients in which intravenous solutions containing dextrose are to be avoided in the immediate postoperative period, our house staff occasionally writes for D5NS or something of the like. As a result, it is not uncommon to encounter high glucose levels in these patients the day after surgery. Were you able to control for these types of variables in your data analysis? Because, if your cohort included patients who received intravenous fluids containing dextrose, for example, your data analysis could have included patients who had fictitious hyperglycemia rather than diabetic hyperglycemia.

Second, did you drill down a bit deeper and look at the type of colorectal resection that took place? For example, did you compare patients undergoing resection of the left colon with those undergoing resection of the right colon? I would hypothesize that an ileocolic resection may lead to a debulking the GLP1-producing cells in the ileum, which may have contributed to your glucose imbalance.

Response From R.P. Kiran:

Whether intravenous solutions might have led to any discrepancies in blood glucose values, we were not able to assess considering the confines of the retrospective design of our study.

Your question, whether the anatomical segment of resected colon was associated with glucose changes, is very thought-provoking. In this study, we did not specifically compare the influence of right versus left colon resection on postoperative glucose level changes.

DISCUSSANTS

A.N. Sidawy (Washington, DC):

We have looked at the effect of perioperative hyperglycemia in vascular patients. In this yet to be published data analysis, we found the following findings, which I would like you to comment on.

First, very interestingly, the nondiabetic patients with perioperative hyperglycemia actually had worse complications than diabetic patients. We thought that this is probably due to diabetic patients being used to hyperglycemic episodes.

Second, we noticed what is referred to as the "U shape" effect, meaning that patients with perioperative hypoglycemia, less than 80 mg/dL, also had higher complication rates than patients who remained normoglycemic perioperatively.

I wonder, concerning normal patients with normal fasting glucose level who spike their blood glucose perioperatively, whether a good number of them are prediabetic.

Response From R.P. Kiran:

We found that nondiabetic patients had similar outcomes as diabetic patients when hyperglycemia developed. Thus, hyperglycemia in nondiabetic patients also leads to deleterious effects. As previously discussed, we did not evaluate the effect of hypoglycemia on outcomes in this study. We agree that it is possible that several of the patients who developed elevated blood glucose values may have been prediabetic. Close monitoring of blood glucose values after colorectal surgery would identify such patients. Previous experience from the diabetic literature supports the management of any elevated postoperative glucose values.

DISCUSSANTS

S.J. Dudrick (Waterbury, CT):

I would like to echo Dr. Polk's comments about the concerns for hypoglycemia. How do you think that we can control glycemia to ensure the optimal results?

Forty or 50 years ago, when we first started working with infusions that led to total parenteral nutrition, clearly, glucose was the biggest problem. And as the glucose was increased in the infusion, sometimes that caused the problems. On the contrary, when we gave a standard amount of sugar to patients postoperatively, the blood glucose level would rise earlier than the white blood cell count would rise, and both of them would rise before the patient would become febrile. So, when we were trying to predict infectious complications or trying to determine when to be concerned about the patient's response to a procedure, clearly, the glucose was the most sensitive marker. I think this is still true today.

The ability of the body cell mass to metabolize glucose is very finely balanced. And it will go out of control quicker as a signal than perhaps anything else that we measure, other than maybe cytokines or mitochondrial particles.

At any rate, I would like to ask you to continue your work and perhaps in a prospective fashion try to control the amount of sugar tightly and monitor it more closely. I know that they are trying to do that in the critical care areas, especially in Europe. But in Europe, they are having problems in some hospitals because the nurses do not like the idea that the physicians want to use pumps to control the rate of infusions precisely. They think that this is an insult to the nursing profession who think that they can control it manually just as well with a gravity drip.

We have all kinds of complicating factors that come into play. And again, 50 years ago, Doug Wilmore and I tried to get the industry to create an online glucose-monitoring system inside of a catheter so that we could measure dextrose, or glucose levels in the blood, online and then have a servocontrol mechanism to slow the pump rate if the glucose went up or to increase the pump rate if the blood glucose level decreased below a programmed lower limit.

Possibly such an apparatus does exist, but it certainly is not available clinically universally for practical, optimal day-to-day care. I hope that this Association, or our individual members, will push forward in the future to try to find a better way to administer our fluids and maintain a normal glucose level. It seems like such a simple, obvious concept. And yet we keep stumbling over it and not insisting that we monitor blood glucose levels online continuously as we would perhaps a diabetic patient with an indwelling pump.

It is a very important thing for you to follow up in the future. Thank you for the work you have been doing, and good luck.

Response From R.P. Kiran:

Thank you, Dr. Dudrick, for your comments. This initial study certainly sets the stage for answering further questions in this very important area of perioperative care.

