Prevalence and Clinical Outcome of Hyperglycemia in the Perioperative in non-Cardiac Surgery

1Anna Frisch, PhD, MD
1Prakash Chandra, MD MS
1Dawn Smiley, MD
2Limin Peng, PhD
3Monica Rizzo, MD
1Chelsea Gatcliffe, BS
1Megan Hudson, BS
1Jose Mendoza, BS
1Rachel Johnson, BS
1Erica Lin, BS
1Guillermo E. Umpierrez, MD

Departments of 1Medicine and 3Surgery, and 2Rollins School of Public Health, Emory University, Atlanta, GA

Short Title: Hyperglycemia and surgery

Correspondance:
Guillermo E. Umpierrez, M.D., Professor of Medicine
E-mail: geumpie@emory.edu

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Background. Hospital hyperglycemia, in patients with and without diabetes has been identified as a marker of poor clinical outcome in cardiac surgery patients. It is not known; however, what is the impact of perioperative hyperglycemia on clinical outcome in general and noncardiac surgical patients.

Methods. This observational study aimed to determine the relationship between pre- and post-surgery blood glucose levels and hospital length of stay (LOS), complications and mortality in 3,184 noncardiac surgical patients consecutively admitted to Emory University Hospital, Atlanta, GA between 1/1/07 and 6/30/07.

Results. The overall 30-day mortality was 2.3%, with nonsurvivors having significantly higher blood glucose levels prior to and after surgery (both, p<0.01) than survivors. Perioperative hyperglycemia was associated with increased hospital and ICU LOS (p<0.001) as well as higher postoperative cases of pneumonia (p<0.001), systemic blood infection (p<0.001), urinary tract infection (p<0.001), acute renal failure (p=0.005), and acute myocardial infarction (p=0.005). In multivariate analysis (adjusted for age, gender, race, surgery severity), the risk of death increased in proportion to perioperative glucose levels; however, this association was significant only for patients without a history of diabetes (p= 0.008) compared to patients with known diabetes (p= 0.748).

Conclusion. Perioperative hyperglycemia is associated with increased length of stay, hospital complications and mortality after noncardiac general surgery. Randomized controlled trials are needed to determine if perioperative diabetes management improves clinical outcome in noncardiac surgical patients.
Patients with diabetes are more likely to undergo surgery than are people without diabetes (1; 2). Surgery in diabetic patients is associated with longer hospital stay, higher health care resource utilization, and greater perioperative mortality than nondiabetic subjects (1-3). The higher morbidity and mortality in diabetic patients relates in part to the heightened incidence of comorbid conditions including coronary heart disease, hypertension, and renal insufficiency (4; 5), as well as the adverse effects of hyperglycemia in clinical outcome (6-8). Evidence from observational studies suggests that in surgical patients, with and without diabetes, improvement in glycemic control positively impacts morbidity and mortality (9; 10). The stronger body of evidence comes from the setting of cardiac surgery and critically ill patients admitted to the ICU. In this setting, perioperative hyperglycemia is associated with an increased rate of deep sternal wound infections, hospital complication, and mortality (11; 12), and improvement of glycemic control reduces the rate of postoperative complications, length of hospital stay, and mortality (8; 12; 13). Similarly, the development of perioperative hyperglycemia has also been shown to be a sensitive predictor of nosocomial infection in small observational studies in general surgery (9; 10; 14). Few studies; however, have reported on the association between glucose levels and hospital mortality in general surgery patients, and it is not known if the severity of hyperglycemia and the timing of hyperglycemia prior to or during the postoperative period lead to the increased mortality and hospital complications. Accordingly, this study aimed to determine i) the relationship between perioperative hyperglycemia and diabetes on clinical outcome (length of hospital stay, need for ICU care, infectious complications, acute renal failure, respiratory failure and myocardial infarction), and ii) determine the impact of perioperative hyperglycemia upon survival after adjusting for known prognostic factors in patients undergoing general noncardiac surgery. We hypothesized that general surgery patients with perioperative hyperglycemia would experience higher hospital complications and mortality compared to patients with normal glucose levels.

METHODS
Medical records from all patients who underwent inpatient noncardiac surgical procedures at Emory University Hospital, a tertiary academic center in Atlanta, Georgia, between 1/1/07 and 6/30/07 were included in the analysis. The patient list was obtained from the operative room electronic medical records. We included patients from general surgery, neurosurgery, surgical oncology, orthopedic, vascular, thoracic, urology, otolaryngology (except tonsillectomy) and gynecology services. Only the first surgical procedure was included in patients with more than one surgery. We excluded patients with outpatient surgical procedures or those with a LOS < 24 hours or with minor surgical procedures including endoscopic procedures and ophthalmologic surgery. The study was approved by the Emory University Institutional Board Review. We collected data on demographics, LOS, 30 day mortality rate, inpatient laboratory values such as whole blood glucose, plasma blood glucose (BG) and creatinine one day before, on day (post-surgery day 1), and within the first 10 days after surgery. Diabetes was defined by ICD9 code (ICD9 250). Hospital complications including myocardial infarction (ICD9 codes: 410.51, 410.71, 410.81, 410.91), pneumonia (ICD9 481, 482, 485, 486), sepsis and bacteremia (ICD9 0.38, 790.7, 785.52, 995.9), skin infection (ICD 9: 681, 682, 685, 686, 707), urinary tract
infection (599.0, 590.8) were identified. Acute renal failure was defined as an increase in serum creatinine > 0.5 mg/dl from baseline during the hospital stay. Mortality rate was assessed in the hospital and within a 30-day period after surgery. The 30-day mortality was captured using hospital records, outpatient medical records and the database from the National Surgical Quality Improvement Program (NSQIP). Severity of surgery was graded as low, intermediate and high based on American College of Cardiology/American Heart Association (ACC/AHA) pre-operative evaluation guidelines (15). High risk procedures included aortic and other major vascular and peripheral arterial surgeries. Intermediate risk included carotid endarterectomy, head and neck, intraperitoneal and intrathoracic, orthopedic, and prostate surgeries. Low risk procedures included superficial (procedures involving skin, skeletal muscle or superficial fat) and breast surgeries.

Data Analysis. Comparison of baseline demographics and clinical characteristics between groups were analyzed by nonparametric Wilcoxon tests for continuous variables. For categorical variables, Chi-square tests were used. Multiple logistic regression and adjusted odds ratios were employed to determine the influence of covariates including demographic and clinical characteristics on mortality rates. Multivariate linear regression was used to study the effects of these covariates on length of stay. A p-value of 0.05 was considered significant.

RESULTS
The original data file consisted of 3588 medical records. We excluded 374 patients with multiple admissions and 30 patients ≥ 90 years of age. The patient population included 3184 patients, 53.8% female and 46.2% male, with mean age 56.5±16 years, and mean BMI 27.6 ± 7.3 kg/m², who underwent noncardiac surgical procedures. Table 1 shows the clinical characteristics of study patients divided into diabetics and non-diabetics. A history of diabetes prior to admission was known in 643 cases (20.2%). Compared to subjects without a history of diabetes, patients with diabetes were older (61.2±13.2 vs. 55.4±15.9 years, p<0.001), had higher BMI (29.6 ± 7.8 vs. 26.8 ± 6.9 kg/m2, p<0.001), were more likely male (52.1 vs. 44.8%, p<0.001), were of minority ethnic groups (Blacks: 28.8 vs. 21.4%, p<0.001), and were more likely to undergo high risk surgical procedures (8.9 vs. 6%, p=0.012). The mean BG prior to surgery in the entire cohort was 120±38 mg/dl. Of note, there were no significant differences in BG concentration between patients included and those excluded in the analysis. As expected, nondiabetic subjects had lower pre-surgery BG levels (113±28 mg/dl) compared to patients with a known history of diabetes (145±51 mg/dl), p<0.001. The mean BG on the first day after surgery was 155±42 mg/dl in diabetics and 132±28 mg/dl in non-diabetic subjects, both values were higher than those reported during the subsequent hospital stay (139±34 mg/dl and 115±21 mg/dl, respectively, p<0.01). After surgery, 40% of patients had a mean BG >140 mg/dl, three fourths of them had a mean BG between 141-180 mg/dl, and the remaining had a BG >180 mg/dl. Clinically significant hyperglycemia (defined as a BG >180 mg/dl) was observed in 7.9% of patients before surgery, 17.2% of subjects on day of surgery, and in 9.9% of patients during the postoperative period (days 2-10).

Mortality and in-hospital complication rates in patients with and without diabetes are shown in Figure 1. The overall 30 day mortality was 2.3% (72 out of 3,112 patients), with a higher mortality (3.1%) observed in diabetics than in non-diabetic (2.1%) patients, but this difference did not reach statistical significance (p=0.105). Compared with
nondiabetic subjects, diabetics had higher rate of complications including pneumonia (12.1% vs. 5.4%; p<0.001), wound and skin infections (5% vs. 2.3%; p<0.001), systemic blood infection (3.6% vs. 1.1%; p<0.001), urinary tract infections (4.5% vs. 1.4%; p<0.001), acute myocardial infarction (2.6% vs. 1.2%; p=0.008), and acute renal failure (ARF) (9.6% vs. 4.8%; p<0.001). In addition, diabetic patients had higher length LOS and ICU LOS than non-diabetic subjects (8.8±10.6 vs. 7±10.8 days, p<0.001 and 2.3±6.2 vs. 1.8±6.5 days, p<0.01, respectively).

The association between glucose levels prior to and after surgery and mortality odds ratio is shown in Figure 2. We found a strong association between mortality and glucose levels both, prior to surgery (2A) and after surgery (2B); however, mortality odds ratios were different between patients with and without diabetes. The risk of death increased in proportion to BG levels in patients without a history of diabetes (p<0.001), but the association of hyperglycemia and mortality was greater in patients without a history of diabetes prior to admission (p<0.001 for both pre-op BG and post-op BG) compared to patients with known diabetes (p=0.78 for pre-op BG and p=0.51 for post-op BG). Multivariate analysis adjusted for age, gender, race, and surgery severity showed that pre-surgery BG may be an independent predictor of mortality with marginal significance (p=0.063), and likewise with post-operative BG concentration (p=0.087). To investigate the effect of race on mortality and hospital complications, we included African American race in the multivariate analyses which adjusted for age, African Americans (AA) ethnicity, diabetes status, interaction between AA and diabetes, gender, severity of surgery, and pre-surgery BG levels. We observed that AA patients were not at increased risk of mortality than other races (p= 0.96), but they were more likely to develop complications including pneumonia (p= 0.0075) and ARF (p= 0.0158) than non AA. We observed no difference in BG concentration prior to or after surgery between racial groups.

The clinical characteristics of survivors and nonsurvivors are shown in Table 2. Compared to survivors, patients who died had significantly higher BG concentration before surgery (133.4±40.9 vs. 119.9±37.7 mg/dl, p=0.002) and after surgery (126.6±23.7 mg/dl vs. 119.7±26.6 mg/dl, p<0.001). In addition, compared to survivors, deceased patients were older (p<0.001), majority of them were males (p<0.001), have a longer hospital LOS (18±24 vs. 7±10 days, p<0.001), had higher rate of acute renal failure (30.6% vs. 5.2%, p<0.001), and bacteremia/sepsis (16.7% vs. 2.2%, p<0.01). In addition, we found that age, male gender, development of hyperglycemia prior to or after surgery, blood infections, and acute myocardial infarction were predictors of 30 day mortality.

DISCUSSION

Our study indicates that perioperative hyperglycemia is associated with increased risk of hospital complications in patients undergoing non-cardiac surgery. Perioperative hyperglycemia significantly increased the risk of pneumonia, systemic blood infections, urinary tract infection, skin infections, and acute renal failure during the postoperative period. In addition, we found a significant association between BG concentration and mortality; however, the impact of hyperglycemia on mortality rate was more important among patients without a history of diabetes compared to those with known diabetes prior to admission.

The association between hyperglycemia and increased risk of hospital complications and mortality in critically ill (1; 8; 12; 13) major cardiovascular surgery patients (12; 16; 17) is well established. Less information is available on the importance of hyperglycemia in general and non-cardiac surgery. Small
observational studies in non-cardiac surgery patients have reported that postsurgical hyperglycemia is associated with infectious complications in general surgery patients (10). In patients with hyperglycemia (BG > 220 mg/dL) on postoperative day one, the infection rate was 2.7 times that observed (31.3% versus 11.5%) in diabetic patients with all serum glucose values < 220 mg/dL (10). When minor infection of the urinary tract was excluded, the relative risk for "serious" postoperative infection (sepsis, pneumonia, and wound infection) increased to 5.7 when any postoperative day one BG was > 220 mg/dL. Ramos et al (14), showed an increase of postoperative infection rate by 30% for every 40 mg/dL rise in postoperative BG levels above 110 mg/dL and increased length of hospital stay in general and vascular surgery patients independent of their diabetes status. The results of our study confirm the association between increased length of hospital stay and risk of hospital complications and mortality in patients with BG levels > 150 mg/dL, particularly in those who did not carry a prior diagnosis of diabetes (7; 18). We and other investigators (7; 19-21) previously reported that the development of hyperglycemia in hospitalized patients without a history of diabetes is an important outcome marker associated with worse clinical outcome compared to those with a previous history of diabetes or with normoglycemia.

To investigate the effect of race on mortality and hospital complications, we included African American race in the multivariate analyses which adjusted for age, diabetes status, gender, severity of surgery, and glucose levels. We observed that African American patients had similar mortality rates than other races (p = 0.96), but they were more likely to develop complications including pneumonia (p = 0.0075) and acute renal failure (p = 0.0158) than non African Americans. We observed no difference in BG concentration prior to or after surgery between racial groups, thus the observed difference in hospital complications cannot be explain by differences in glycemic control among racial groups. This observation needs to be confirmed in future studies in different inpatient clinical settings with particular attention to severity of illness and presence of comorbidities. The reasons for poor outcome with high blood glucose levels remain unclear. Much of the attention has focused on increased rate of infections and poor wound healing (1; 22). Hyperglycemia is associated with impaired leukocyte function, including decreased phagocytosis, impaired bacterial killing and chemotaxis (23). Hyperglycemia has also been shown to impair collagen synthesis and to impair wound healing among patients with poorly controlled diabetes (22). Acute hyperglycemia activates oxidative pathway through increased generation of Reactive Oxygen Species (ROS). ROS causes direct tissue damage by lipid oxidation and neutralizes Nitric Oxide (NO) which impairs vasodilation and reduces tissue perfusion (24). Proinflammatory pathway is also activated through NF-kB activation. This leads to production of inflammatory cytokines like TNF-alpha, IL-6, plasminogen activator inhibitor-1 (PAF-1) which causes increased vascular permeability, and leukocyte and platelet activation (24). Similarly, acute hyperglycemia and oscillating glucose levels have been shown to cause higher levels of oxidative stress and endothelial dysfunction than chronic and sustained hyperglycemia (25).

The main limitation of this study is its retrospective nature. Our study did not address the question of whether treatment of hyperglycemia may reduce hospital complications or mortality during the perioperative period. Although several prospective randomized trials in patients undergoing coronary bypass surgery have shown that aggressive glycemic control
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reduces short- and long-term mortality and systemic infections, it is not clear if intensified insulin therapy in general surgery will improve clinical outcome and lower mortality. Our group is currently conducting a prospective, randomized trial of strict glycemic control to address these issues (NCT 00596687).

In summary, perioperative hyperglycemia is associated with increased in-hospital morbidity, hospital and ICU LOS, and mortality. Hyperglycemia as well as age, sepsis, pneumonia, acute renal failure, acute myocardial infarction were other important predictors of mortality. These results suggest that hyperglycemia is harmful and should be treated during the perioperative period in general surgical patients. The fact that patients without a history of diabetes (stress hyperglycemia) experience worse outcome and higher mortality at a same glucose level than those with known history of diabetes suggest a lack of adaptation to acute hyperglycemia and its associated inflammatory and oxidative state. Our results underscore the need for prospective trials assessing impact of glycemic control during the perioperative period in surgery patients.

Authors Contributions: (A.F.) designed the study, collected and interpreted data, (P.C.) did critical analysis, (D.W., M.R.) collected data and wrote manuscript, L.P. did statistical analysis, (C.G., M.G., J.M., R.J., E.L.) recruited subjects and collected data, (G.U.) designed study, did critical analysis and wrote manuscript.

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Figure Legends.
Figure 1. Thirty day mortality and in hospital complication rates in patients with and without diabetes. Blood infection: combined bacteremia and sepsis; urinary tract infection (UTI), acute myocardial infarction (AMI), acute renal failure (ARF).
Figure 2. Mean blood glucose concentration after surgery and odds Ratio for 30 day mortality in patients with and without diabetes.

REFERENCES


Table 1. Patient Characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Non diabetic</th>
<th>Diabetic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>3,112</td>
<td>2469 (80)</td>
<td>643 (20)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>56.5±16</td>
<td>55.4±15.9</td>
<td>61.2±13.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1712 (53.8)</td>
<td>1404 (55.2)</td>
<td>308 (47.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>1472 (46.2)</td>
<td>1137 (44.8)</td>
<td>335 (52.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.6 ± 7.3</td>
<td>26.8 ± 6.9</td>
<td>29.6 ± 7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasians, n (%)</td>
<td>2161 (71.5)</td>
<td>1756 (73.2)</td>
<td>405 (65.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>African Americans, n (%)</td>
<td>693 (23)</td>
<td>514 (21.4)</td>
<td>179 (28.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanics, n (%)</td>
<td>40 (1.3)</td>
<td>32 (1.3)</td>
<td>8 (1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severity of Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk, n (%)</td>
<td>268 (8.4%)</td>
<td>224 (8.8)</td>
<td>44 (6.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Moderate risk, n (%)</td>
<td>2707 (85%)</td>
<td>2165 (85.2)</td>
<td>542 (84.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>High risk, n (%)</td>
<td>209 (6.6%)</td>
<td>152 (6)</td>
<td>57 (8.9)</td>
<td>0.012</td>
</tr>
<tr>
<td>BG before surgery, mg/dl</td>
<td>120.4 ± 37.9</td>
<td>112.6 ± 28.2</td>
<td>144.7 ± 51.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BG on the day of surgery, mg/dl</td>
<td>137.6±33</td>
<td>132.2±27.6</td>
<td>154.6±41.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average BG after surgery, mg/dl</td>
<td>119.9±26.5</td>
<td>114.5±21.2</td>
<td>139.3±33.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital length of stay, days</td>
<td>7.4±10.8</td>
<td>7±10.8</td>
<td>8.8±10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality at 30 days, n (%)</td>
<td>72 (2.26)</td>
<td>52 (2.05)</td>
<td>20 (3.11)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 2. Clinical Characteristics among Survivors and Nonsurvivors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (3112, 98.1%)</th>
<th>Non-survivors (72, 9.7%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>56 ± 16</td>
<td>65 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male/Female (%)</td>
<td>46/54</td>
<td>67/33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood glucose, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Before surgery</td>
<td>118 ± 38</td>
<td>132 ± 42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Day of surgery</td>
<td>138 ± 32</td>
<td>143 ± 28</td>
<td>0.028</td>
</tr>
<tr>
<td>- After surgery (days 2-10)</td>
<td>122 ± 28</td>
<td>130 ± 27</td>
<td>0.007</td>
</tr>
<tr>
<td>Acute renal failure, n(%)</td>
<td>163 (5.2)</td>
<td>22 (30.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>194 (6.2)</td>
<td>22 (30.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>95 (3)</td>
<td>14 (19.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute MI</td>
<td>65 (2)</td>
<td>7 (9.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS, days</td>
<td>7.2 ± 10.8</td>
<td>18 ± 24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU LOS, days</td>
<td>1.8 ± 6.4</td>
<td>14.7±23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure 1

† p: NS, ‡ p: 0.017, * p: < 0.001
Figure 2a

- All patients
- Diabetics
- non-Diabetics

Figure 2b

- All patients
- Diabetics
- non-Diabetics