Effect of Average Blood Glucose Greater Than 140 mg/dL on Adverse Patient Outcomes in Adult Medical/Surgical Patients

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ABSTRACT

Background: In hospitalized patients, hyperglycemia is defined as blood glucose greater than 140 mg/dL. Hyperglycemia can lead to the development of nosocomial infections as well as cardiovascular events. Despite these risks, current guidelines recommend blood glucose be maintained between 140-180 mg/dL. Previous studies have shown that elevated blood glucose levels are associated with increased patient mortality. However, these studies assessed blood glucose at a single point in time.

Objective: The primary objective of this study is to determine the impact of average blood glucose >140 mg/dL on a composite outcome of intensive care unit transfer, death, length of stay > 4 days, development of nosocomial infection, or new cardiovascular event (myocardial infarction [MI], ischemic stroke, deep vein thrombosis [DVT], pulmonary embolism [PE], or new onset heart failure) occurring during patient admission.

Methods: This single centered, randomized, case-control, retrospective chart review sorted adult medical/surgical patients into two groups, average blood glucose ≤140 mg/dL or >140 mg/dL, of 120 patients each.

Results: Forty-seven (39.2%) patients in the >140 mg/dL group experienced the primary composite outcome versus 27 (22.5%) patients in the ≤140 mg/dL group (p=0.005). Secondary outcomes found that patients with diabetes in the >140 mg/dL group were more likely to experience the primary outcome than those in the ≤140 mg/dL group (41 (48.8%) vs 3 (13.6%) p=0.003).

Conclusions: This study found that medical/surgical patients with an average blood glucose >140 mg/dL may be at an increased risk of developing adverse patient outcomes.

Keywords: diabetes, internal medicine, patient outcomes

BACKGROUND

In hospitalized patients, hyperglycemia is defined as blood glucose greater than 140 mg/dL.¹ In patients with diabetes, hyperglycemia is caused by either an absolute or relative deficiency of insulin due to either a lack of pancreatic β-cell function or decreased function combined with increased insulin resistance.¹ Even in patients without diabetes, acute illness, surgery or trauma can cause stress hyperglycemia via activation of cortisol and epinephrine. These hormones increase gluconeogenesis, inhibit β-cell insulin release, and decrease glucose uptake which can impact disease severity and overall mortality.² ³ Left untreated, elevated blood glucose levels can lead to detrimental patient outcomes including infection, stroke, venous thromboembolism, increased hospital length of stay and increased mortality.⁵ Patients without a known diagnosis of diabetes are at highest risk of these adverse outcomes.⁴ ⁶ Hospitalized patients are also predisposed to an increased risk of clot development due to immobility and/or disease pathophysiology.⁷ Hyperglycemia produces the previously mentioned outcomes through altered tissue metabolism, increased oxidative stress, immunosuppression, impaired wound healing and thickening of capillary basement membranes which contributes to hypercoagulability.² ³ The current 2020 American Diabetes Association guidelines recommend that for patients who are hospitalized, blood glucose should be maintained between 140-180 mg/dL.³ This recommendation is supported by evidence of an increased risk of death seen from hypoglycemia (blood glucose ≤70 mg/dL). However, studies supporting this recommendation were conducted predominantly in the critical care population and may not reflect the general medical/surgical patient population.¹ ⁸

Previous studies have reported the incidence of hyperglycemia in all patients admitted to community hospitals to be between 32% and 38% regardless of diabetes diagnosis.⁶ ⁹ ¹⁰ Furthermore, available literature regarding the inpatient management of blood glucose in medical/surgical populations have focused on single blood glucose values and have not assessed overall glycemic control demonstrated by average blood glucose.⁶ ¹¹ ¹² ¹³ Measuring average blood glucose can provide a better picture of a patient’s overall glycemic control during hospitalization and may be able to better predict likelihood of adverse patient outcomes related to hyperglycemia. The objective of this study is to determine if general medical/surgical patients having an average blood glucose >140 mg/dL is correlated with an increased risk of adverse patient outcomes during hospital admission.
METHODS
This was a single-center, randomized, case-control, retrospective chart review conducted in a 117-bed community hospital. This study was approved with full waiver of consent via expedited review by the institution’s Institutional Review Board (STUDY20180827). All patients over 18 years old admitted to medical/surgical care units between January 1, 2018 and May 31, 2018 were eligible for inclusion. Patients were excluded if they were admitted directly to the critical care or birth center units, had no blood glucose measurement during their admission, were pregnant or nursing, or were placed into hospice care or comfort measures only care within 24 hours of admission. Overall, there were 4,045 patient admissions during the study period. Six hundred and forty-six of those admissions were readmissions for the same patient and subsequently excluded. The remaining 3,399 patients were then utilized as a database from which to select patients for inclusion based on the aforementioned criteria. Each patient was assigned a number from 1-3,399. A random number generator from Microsoft Excel (Microsoft Corporation, Redmond, WA) was then used to select patients for evaluation and inclusion into the study. Patients who, after evaluation, met inclusion criteria were then assigned to two groups, average blood glucose ≤140 mg/dL or average blood glucose >140 mg/dL. Patients were evaluated until each group included 120 patients. All blood glucose values documented in the electronic medical record for the inpatient admission of each patient were collected via manual chart review, summed then divided by the number of entries to obtain the average blood glucose for the entire admission. These values included both point-of-care blood glucose readings and laboratory draws that reported blood glucose results. Fasting and post-prandial readings were not differentiated and no weighting or adjustments to values were performed. Baseline characteristics assessed included age, height, weight, race, gender, provider documented discharge diagnosis and diabetes diagnosis. A list of any medication known to affect blood glucose either through direct mechanism of action or via known side effects that were reported as blood glucose results. Fasting and post-prandial readings were not differentiated and no weighting or adjustments to values were performed. Baseline characteristics assessed included age, height, weight, race, gender, provider documented discharge diagnosis and diabetes diagnosis. A list of any medication known to affect blood glucose either through direct mechanism of action or via known side effects was recorded. Also recorded was any hypoglycemic event that required treatment with documented administration of oral glucose, intramuscular or intravenous glucagon or intravenous dextrose. Charlson Comorbidity scores were also calculated for each patient. The Charlson Comorbidity score weighs various comorbidities, including diabetes, by their severity and total score is predictive for 1-year mortality rate. Scores ≥5 were found to have an 85% 1-year mortality rate, though this percentage is likely to have decreased with medical advances in the thirty-three years since this study was published. The primary outcome was a composite of transfer to the intensive care unit, death from any cause, length of stay > 4 days which is the average length of stay for this hospital, development of nosocomial infection defined as new onset infection occurring >48 hours after hospital admission, new cardiovascular event (myocardial infarction [MI], ischemic stroke, deep vein thrombosis [DVT], pulmonary embolism [PE], or new onset heart failure). Secondary outcomes were the rates of each individual outcome outlined above and a subgroup analysis of the composite outcome by diagnosis of diabetes. All study outcomes were determined via manual chart review of the electronic medical record including nursing and provider documentation and admit, discharge, transfer data.

Statistical Analysis
Baseline characteristics of the study population were analyzed using student t-tests and chi-square tests. The primary composite outcome was analyzed using a chi-square test. The secondary outcomes were all analyzed with either chi-square or Fisher’s exact tests as appropriate. Prior studies have identified a background risk for mortality and increased length of stay to be 41%; this risk was increased to 60% in patients with elevated blood glucose levels. In order to achieve 60% incidence, 120 patients were needed in each group to meet 80% power. Alpha was set at p=0.05 for significance. Inclusion in each group was capped at 120 patients. For statistical comparison purposes, discharge diagnoses were gathered into 12 broad categories determined by investigator: cardiovascular, endocrine, gastrointestinal, genitourinary, hematologic, infection, oncologic, other, poisoning, respiratory, substance use/overdose, and surgery.

RESULTS
A total of 606 patients were evaluated from the 3,399 patient database for inclusion, and 366 of those patients were excluded from the study due to predetermined exclusion criteria (Figure 1). At baseline, 240 medical/surgical patients were included in the study, 120 in the ≤140 mg/dL group and 120 patients were included in the >140 mg/dL group. (Table 1). Medical patients made up 217 (90.4%) of the patient population.

Regarding the primary composite outcome, 74 patients experienced the composite primary outcome during the study period, with the primary outcome occurring in 27 in the ≤140 mg/dL group and 47 in the >140 mg/dL group (p=0.005). No patients in the study developed a DVT, PE or new onset heart failure; 1 patient experienced an MI and 1 patient experienced a stroke, both were in the >140 mg/dL group (Table 2). Death and nosocomial infection were not significantly different between groups. Two patients in the ≤140 mg/dL group were transferred to the ICU vs 11 in the >140 mg/dL group (p=0.01). The average length of stay for entire study population was 3.89 days; 3.56 days for the ≤140 mg/dL group and 4.29 days for the >140 mg/dL group. There was a significant difference in length of stay > 4 days between groups, with 25 patients in the ≤140 mg/dL group vs 43 in the >140 mg/dL group having a length of stay > 4 days (p=0.01).

For the subgroup analysis, a total of 106 patients with diabetes were evaluated; 22 patients were in the ≤140 mg/dL group and the remaining 84 were in the >140 mg/dL group (Table 2). Regarding patients with diabetes who experienced the primary
composite outcome, this outcome occurred in 3 in the ≤140 mg/dL group and 41 in the >140 mg/dL group (p=0.003).

DISCUSSION
This retrospective case-control study found that medical/surgical patients with an average blood glucose >140 mg/dL during hospitalization were associated with an increased risk of developing adverse patient outcomes, notably intensive care unit transfer or increased hospital length of stay.

Previous studies that have been conducted in general medical/surgical populations include a study by Noordzij et al. who evaluated 2,151 patients undergoing non-cardiac, non-vascular surgeries.11 The authors determined that elevated blood glucose (pre-operative blood glucose >100 mg/dL) resulted in an associated increase in 30 day all-cause mortality with an adjusted odds ratio (aOR) of 1.7 (95% Confidence Interval (CI) 1.40-2.10, p<0.001) for patients with blood glucose 101-200 mg/dL and aOR 2.1 (95% CI 1.30-3.50 p<0.001) for blood glucose >200 mg/dL.11 This current study reached similar conclusions as Noordzij et al. despite using a higher blood glucose cutoff of 140 mg/dL. However, it should also be noted that this study used a composite endpoint of predetermined outcomes whereas Noordzij et al. specifically used mortality as the primary outcome and included almost ten times as many patients.

Bruno et al. had similar findings in a retrospective case-control study of 6,676 inpatients.12 Patients with admission blood glucose between 100-200 mg/dL were at increased risk of in-hospital mortality, aOR 1.32 (95% CI 1.22-1.43).12 Notably, patients with blood glucose between 60-80mg/dL were also at increased risk of in-hospital mortality, OR 1.06 (95% CI 1.04-1.07).13 The study by Bruno et al. included a significantly larger patient population compared to this study and assessed a singular endpoint rather than a composite outcome. However, the results further confirm the findings in this study that patients with elevated blood glucose values are at higher risk of adverse patient outcomes including mortality.

Baker et al. conducted a retrospective study in 284 patients admitted with an exacerbation of chronic obstructive pulmonary disease.13 The study divided patients into quartiles (blood glucose <110 mg/dL, 110-125 mg/dL, 126-160 mg/dL and >160 mg/dL) based on their maximum blood glucose level during their hospitalization. The quartile used as a comparator was blood glucose <110 mg/dL. The primary endpoint was a composite of mortality and length of stay > 9 days, which was the average length of stay for the study population. The study found that for patients in the quartile of blood glucose 110-125 mg/dL, elevations in blood glucose were not associated with a significant difference in the primary outcome. However, patients in the quartiles of blood glucose 126-160 mg/dL and >160 mg/dL were both at increased risk of mortality or increased length of stay, relative risk (RR) 1.46 (95% CI 1.05-2.02) and RR 1.97 (95% CI 1.33-2.92), respectively.13 The endpoints of this study and Baker et al. were both composite endpoints of adverse patient outcomes. This study offers further evidence to support the findings of Baker et al. by finding that medical/surgical patients are at increased risk of adverse outcomes. However, the average length of stay in the study by Baker et al. was 9 days whereas this study used 4 days for a length of stay comparator which may have influenced the amount of patients who met criteria for an increased length of stay.

Umpierrez et al. conducted a retrospective chart review and assessed in-hospital mortality of inpatients (2,030). In this study, patients were divided into three groups based upon blood glucose [normoglycemia, hyperglycemia (fasting blood glucose >126 mg/dL or random blood glucose >200 mg/dL on 2 separate occasions) with known diabetes, or hyperglycemia with no known diabetes]. Patients with hyperglycemia and no known diabetes expressed a 16% in-hospital mortality rate compared to 3% in patients with known diabetes (p<0.001) and 1.7% in patients with normoglycemia (p<0.001).6 The findings of Umpierrez et al. contrast this study by demonstrating that the risk of death was not increased in hyperglycemic patients with known diabetes.6 There could be many factors that contribute to this difference including patient population (urban vs. rural in this institution) and the single-center nature of both studies. Different criteria for hyperglycemia were used which could affect the overall results. However, the average blood glucose was much higher in the study by Umpierrez et al. (189 mg/dL and 230 mg/dL versus 187 mg/dL in this study). The study by Umpierrez et al. also assessed consecutive patients while this study analyzed a random sample of patients during a longer period of time. The study population assessed by Umpierrez et al. was younger and additionally, comorbidities were collected but differences between study groups was not reported.

Sahni et al. conducted a retrospective review of 30-day readmission or mortality based on last recorded blood glucose before discharge.17 67,308 patients were stratified into seven groups based on last recorded blood glucose prior to discharge; <70 mg/dL, 70-100 mg/dL (control group), 100-150 mg/dL, 150-200 mg/dL, 200-300 mg/dL, 300-400 mg/dL and >400 mg/dL. The study found that patients adjusted relative risk of readmission or mortality increased as blood glucose increased. The 100-150 mg/dL group had a 1.08 adjusted relative risk increasing to a 2.51 adjusted relative risk for the >400 mg/dL group compared to the 70-100 mg/dL group.17 The study also found that patients with a prior diagnosis of diabetes had a lower risk of 30 day readmission or mortality compared to those who did not (100–150 mg/dL: 9.6% versus 8.1%, 150–200 mg/dL: 23.2% versus 16.9%; p < 0.05). The findings by Sahni et al. were similar to the findings in this study that risk of adverse patient outcomes is elevated with higher blood glucose levels. The study by Sahni et al. supports the previously discussed results found by Umpierrez et al. that patients without diabetes are at higher risk of adverse patient outcomes compared to
those with diabetes at similar levels of hyperglycemia. The results of this study did not reach a similar conclusion but could be limited due to the smaller patient population (240 vs 2,030 vs 67,308).6,17

This study adds to the limited literature of glycemic control in the medical/surgical setting by confirming the findings of Noordzij et al, Bruno et al, and Baker et al, and additionally identifying that average blood glucose during hospitalization is associated with an increased risk of experiencing adverse patient outcomes rather than evaluating a single blood glucose value.5,11-13

There were several strengths of this study. Baseline characteristics were predominantly well matched, with the exception of differences in the Charlson Comorbidity score, diabetes diagnosis and medications that affect blood glucose levels between groups. However, given the considerable number of patients with diabetes evaluated in this trial, patients with uncomplicated diabetes of any type are given 1 point on the Charlson Comorbidity Index which likely accounts for the 1-point difference between groups. Additionally, patients with known diabetes are likely taking anti-hyperglycemic therapies which could explain the difference found in the use of medications that affect blood glucose values. This study also selected a randomized population which can help to account for seasonal differences in comorbid illnesses and glucose control.

Limitations of this study include a small sample size which was limited to a single rural medical center. The study population was almost exclusively Caucasian patients which limits the overall generalizability of this study. This study also did not factor nutritional status, fasting states and timing of blood glucose measurement into the average blood glucose analysis. Patients who received glucose to correct hypoglycemia may also have a falsely higher average blood glucose due to this correction. However, the number of patients treated was not significantly different between groups. Additionally, the study did not differentiate between types of medications that affected blood glucose, including what specific home regimens patients with pre-existing diabetes may have been on. This study also did not factor in length of time since diabetes diagnosis which could have increased the rate of adverse patient outcomes in patients who have been poorly controlled for an extended period of time. Additionally, this study did not address why patients were transferred to the intensive care unit, which per institutional policy, could have included the need for intensive glycemic management with continuous insulin infusion. The retrospective chart review nature of the study provides inherent limitations because the results are dependent on what is documented in the electronic medical record. While this study has confirmed previous findings, it is retrospective in nature and cannot definitively determine that elevated average blood glucose is the cause of adverse patient outcomes. A randomized controlled trial of medical/surgical patients should be conducted to assess the outcomes of tighter glycemic control in this setting.

**CONCLUSION**

In conclusion, this study demonstrates that in hospital hyperglycemia, defined as an average blood glucose >140 mg/dL, may be a risk for the development of poor patient outcomes in medical/surgical patients. This risk is maintained when patients with diabetes were analyzed separately. As the average blood glucose in the >140 mg/dL group was above the upper limit recommended by the American Diabetes Association maintaining appropriate glucose control during the patients stay can help to mitigate this risk.3 However, this study adds to the limited evidence of glycemic control in medical/surgical populations and necessitates the need for larger prospective randomized controlled trials assessing the outcomes in patients without diabetes with tighter glucose control.

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**Treatment of Human Subjects:** This study was approved with full waiver of consent via expedited review by the University Hospitals’ Institutional Review Board (STUDY20180827).

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Figure 1. Study Inclusion

4045

- Patient database

646

- Patients excluded due to readmission

3399

- Filtered patient database

606

- Patients evaluated for study inclusion

240

- Patients included in study analysis

120

- ≤140 mg/dL

120

- >140 mg/dL

366

- Patients excluded from study

104 admitted to birth center or newborn
44 admitted to critical care unit
10 no blood glucose
8 admitted prior to, or discharged after study period
200 met inclusion criteria but group enrollment exceeded 120
Table 1. Baseline Characteristics

| Baseline Characteristic               | Study (n=240) | ≤140 mg/dL (120) | >140 mg/dL (120) | p-value |
|--------------------------------------|--------------|-----------------|-----------------|---------|
| Age (Yrs)                            |              |                 |                 |         |
|                                      | 66.93 (19-95)| 66.33 (19-94)   | 67.54 (33-95)   | 0.544   |
| Mean Body Mass Index                 |              |                 |                 | 0.013   |
|                                      | 31.22        | 29.85           | 32.6            |         |
| Gender [n (%)]                       |              |                 |                 | 0.518   |
| Male                                 | 125 (52.1)   | 65 (54.2)       | 60 (50)         |         |
| Race [n (%)]                         |              |                 |                 | 0.255   |
| Caucasian                            | 232 (96.7)   | 118 (98.3)      | 114 (95)        |         |
| Black                                | 6 (2.5)      | 2 (1.7)         | 4 (3.3)         |         |
| Other                                | 2 (0.8)      | 0               | 2 (1.7)         |         |
| Diabetes [n (%)]                     |              |                 |                 | <0.001  |
|                                      | 106 (44.2)   | 22 (18.3)       | 84 (70)         |         |
| Average Blood Glucose (mg/dL) (SD)   | 149.75 (52.83)| 112.04 (41.18) | 187.46 (52.83) |         |
| Medications Affecting Blood Glucose [n (%)] | 221 (92.1) | 104 (86.7) | 117 (97.5) | 0.002 |
| Average Charlson Comorbidity Score   | 4.85         | 4.26            | 5.45            | 0.002   |
| Treatment for Hypoglycemia [n (%)]   | 6 (2.5)      | 1 (0.8)         | 5 (4.2)         | 0.098   |
| Discharge Diagnosis [n (%)]          |              |                 |                 | 0.221   |
| Cardiovascular                       | 79 (32.9)    | 45 (37.5)       | 34 (28.3)       |         |
| Endocrine                            | 2 (0.8)      | 0               | 2 (1.7)         |         |
| GI                                   | 16 (6.7)     | 7 (5.8)         | 9 (7.5)         |         |
| GU                                   | 7 (2.9)      | 3 (2.5)         | 4 (3.3)         |         |
| Hematologic                          | 2 (0.8)      | 2 (1.7)         | 0               |         |
| Infection                            | 71 (29.6)    | 33 (27.5)       | 38 (31.7)       |         |
| Oncologic                            | 4 (1.7)      | 2 (1.7)         | 2 (1.7)         |         |
| Other                                | 13 (5.4)     | 6 (5)           | 7 (5.8)         |         |
| Poisoning                            | 2 (0.8)      | 2 (1.7)         | 0               |         |
| Respiratory                          | 17 (7.1)     | 6 (5)           | 11 (9.2)        |         |
| Substance Use/Overdose               | 4 (1.7)      | 4 (3.3)         | 0               |         |
| Surgery                              | 23 (9.6)     | 10 (8.3)        | 13 (10.8)       |         |
### Table 2. Study Outcomes*

| Primary Composite Outcome | Study (240) | ≤140 mg/dL (120) | >140 mg/dL (120) | p-value |
|---------------------------|-------------|------------------|------------------|---------|
| Yes                       | 74 (30.8)   | 27 (22.5)        | 47 (39.2)        | 0.005   |

**Secondary Outcomes**

|                   | Study (240) | ≤140 mg/dL (120) | >140 mg/dL (120) | p-value |
|-------------------|-------------|------------------|------------------|---------|
| Death [n (%)]     | 7 (2.9)     | 2 (1.7)          | 5 (4.2)          | 0.25    |
| ICU Transfer [n (%)] | 13 (5.4)  | 2 (1.7)          | 11 (9.2)         | 0.01    |
| Nosocomial Infection [n (%)] | 13 (5.4) | 6 (5.0)          | 7 (5.8)          | 0.776   |
| MI [n (%)]        | 1 (0.4)     | 0                | 1 (0.8)          | 0.316   |
| Stroke [n (%)]    | 1 (0.4)     | 0                | 1 (0.8)          | 0.316   |
| DVT [n (%)]       | 0           |                  |                  |         |
| PE [n (%)]        | 0           |                  |                  |         |
| Heart Failure [n (%)] | 0          |                  |                  |         |
| LOS > 4 Days [n (%)] | 68 (28.3) | 25 (20.8)        | 43 (35.8)        | 0.01    |

**Subgroup Analysis**

| Primary Composite Outcome | Study (240) | ≤140 mg/dL (120) | >140 mg/dL (120) | p-value |
|---------------------------|-------------|------------------|------------------|---------|
| With Diabetes Diagnosis [n (%)] | 106         | 22               | 84               | 0.003   |
| Yes                       | 44 (41.5)   | 3 (13.6)         | 41 (41.8)        |         |
| Without Diabetes Diagnosis [n (%)] | 134        | 98               | 36               | 0.336   |
| Yes                       | 30 (22.4)   | 24 (24.5)        | 6 (16.7)         |         |

*Composite outcome of: intensive care unit transfer, death, length of stay > 4 days, development of nosocomial infection, or new cardiovascular event (myocardial infarction [MI], ischemic stroke, deep vein thrombosis [DVT], pulmonary embolism [PE], or new onset heart failure).