


Analysis of Glucose Levels in Patients Hospitalized With COVID-19 During the First Phase of This Pandemic in West Texas

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Abstract

Background: Patients with hyperglycemia during hospitalization, especially during ICU hospitalizations, often have worse outcomes, even if they do not have a pre-morbid diagnosis of diabetes. High glucose levels can provide insight into the underlying pathogenesis of a disease and can contribute to tissue injury. Some patients with COVID-19 have hyperglycemia during hospitalizations. **Methods:** The Infectious Disease and Control office at University Medical Center in Lubbock, Texas, provided a list of patients with a COVID-19 infection hospitalized between March 1 and May 15, 2020. The medical records were reviewed to collect information on age, gender, history of diabetes, and glucose levels on admission and through the first 7 days of hospitalization. **Results:** This study included 63 patients with a mean age of 62.1 ± 14.1 years. Thirty-five patients (55.6%) were males. The in-hospital mortality rate was 30.2%. The mean admission glucose level was 129.4 ± 57.1 mg/dL in patients who survived (N=47) and 189.6 ± 112.2 mg/dL in patients who died during hospitalization (N=16, $P=.007$). An admission glucose greater than 180 mg/dL predicted mortality in a model adjusted for a diabetes, age, and male gender. The mean differences between the maximum and minimum glucose levels calculated over the first 7 days of hospitalization were 112.93 ± 115.4 (N=47) in patients who survived and were 240.5 ± 97.7 (N=15) in patients who died during hospitalization ($P=.0003$). A difference between the maximum and minimum glucose level greater than 105 mg/dL was associated with increased mortality. **Conclusions:** Patients who died during hospitalization for COVID-19 had higher admission glucose levels than patients who survived. Larger differences between maximum and minimum glucose levels during the first 7 days of hospitalization were associated with increased mortality. These results suggest that high glucose levels identify patients at increased risk for mortality and warrant more study.

Keywords

COVID-19, glucose, glucose variability, outcomes, mortality

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Introduction

Admission glucose levels have significant associations with outcomes in hospitalized patients, and high glucose levels predict increased lengths of stay and increased mortality.^{1,2} In patients with sepsis, hyperglycemia predicts increased mortality and the development of organ dysfunction.³ These high glucose levels may identify prehospitalization comorbidity, such as diabetes or adverse effects from drugs such as corticosteroids, and/or can represent an acute stress response associated with severe illness. Hyperglycemia has direct metabolic consequences, including changes in electrolytes and osmotic diuresis, and contributes to the pathogenesis of diseases, such as sepsis and acute respiratory

failure.⁴ The formation of advanced glycation end products modifies the extracellular matrix and can cause pro-inflammatory responses after binding to receptors on cells, such as macrophages.⁵ In infections with the possibility of systemic involvement, hyperglycemia may result from direct

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infection of the pancreas. Consequently, analysis of glucose patterns and levels in patients with COVID-19 seems important to determine whether or not the hyperglycemia is a risk factor for poor outcomes and whether or not the frequent development of hyperglycemia warrants more study of pancreatic tissue for direct viral involvement. This study analyzes the association between admission glucose levels and glucose fluctuations during hospitalization and mortality in patients hospitalized with COVID-19.

Methods

Medical Record Review

A list of patients with COVID-19 infections established by PCR tests was obtained from the Infection Control and Prevention Office at University Medical Center in Lubbock, Texas. The PCR tests used in our hospital include Xpert[®] Xpress SARS-CoV-2 (Cepheid, Sunnyvale, CA), The BD SARS-CoV-2 Reagents for BD MAX[™] System (Becton, Dickinson and Company, Sparks, Maryland), and The DiaSorin Molecular Simplexa[™] COVID-19 Direct real-time RT-PCR (DiaSorin Molecular LLC, Cypress, California). The timeframe for hospitalization for these patients ranged from March 1, 2020, through a May 15, 2020, discharge date. Medical records were reviewed to determine demographic characteristics, the initial site of hospitalization (inpatient ward service versus intensive care unit), and the mortality outcome. Multiple glucose levels were recorded, including the admission glucose level and the maximum and minimum glucose levels through day 7 of hospitalization. The range in glucose values was calculated by subtracting the minimum glucose value from the maximum glucose value for each patient for all patients who had at least 2 glucose readings. One deceased patient had only 1 glucose reading recorded and was excluded from analysis of glucose range. Hyperglycemia at admission was defined as glucose ≥ 180 mg/dL. Glucose range is dichotomized at the median of 105 mg/dL.

Statistical Analysis

Statistical analysis was performed using Stata 15.1. Results were summarized using means and standard deviations, medians and interquartile ranges, and numbers with percentages. Differences in glucose levels between patients who died and patients who survived were compared using *t*-tests. Logistic regression is used to predict the dichotomous variable indicating mortality. Statistical significance was set at $\alpha < .05$.

Study Approval

This study was approved by the Institutional Review Board (L20-172) at Texas Tech University Health Sciences Center

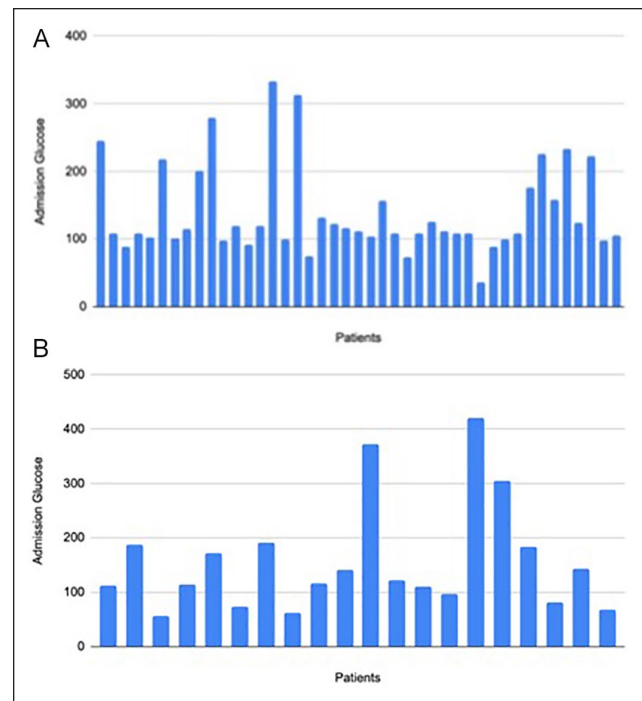


Figure 1. Illustrates the admission glucose levels in patients admitted to an inpatient hospital ward (A) and patients admitted to the medical intensive care unit (B).

in Lubbock, Texas, and by administrative review at University Medical Center in Lubbock, Texas.

Results

This study included 63 patients with a mean age of 62.1 ± 14.1 years. Thirty-five patients (55.6%) were males. The in-hospital mortality rate was 30.2%. The mean length of stay was 10.2 days.

The mean admission glucose level was 129.4 ± 57.1 mg/dL in patients who survived hospitalization ($N=47$) and 189.6 ± 112.2 mg/dL in patients who died during hospitalization ($N=16$, $P=.007$). Figure 1 illustrates the admission glucose values in patients admitted to an inpatient hospital service (A) and in patients admitted to the medical intensive care unit (B). The admission glucose level as a continuous variable did not predict mortality in a multivariable model that included a history of diabetes, age, and male gender (Table 1). An admission glucose of 180 mg/dL or greater was associated with 9-fold higher odds of mortality in a model adjusted for the same variables (Table 1). The maximum glucose level during the first 7 days of hospitalization was 204.2 ± 112.5 mg/dL in patients who survived hospitalization ($N=47$) and 297.2 ± 108.6 mg/dL in patients who died during hospitalization ($N=16$, $t=-2.88$, $P=.006$).

The mean glucose range was 112.93 ± 115.4 mg/dL ($N=47$) in patients who survived hospitalization and was 240.5 ± 97.7 mg/dL ($N=15$) in patients who died during

Table 1. Association Between Admission Glucose Values and Mortality.

	OR	95% CI	P value
Admit glucose value (continuous)	1.01	1.00, 1.02	.105
Diabetes	2.81	0.67, 11.79	.157
Age	1.05	0.99, 1.11	.085
Male	3.90	0.85, 17.84	.079
Pseudo r-squared = 0.20			
Admit glucose \geq 180 mg/dL	9.45	1.71, 52.32	.01*
Diabetes	1.74	0.36, 8.34	.491
Age	1.07	1.00, 1.14	.04
Male	4.09	0.84, 19.79	.08
Pseudo r-squared = 0.27			

*Bold numbers are less than 0.05.

Table 2. Adjusted Logistic Regression Odds Ratios for Glucose Range as a Predictor of Mortality in COVID-19 Patients.

	OR	95% CI	P value
Range (max-min glucose)	1.01	1.00, 1.01	.007*
Age	1.02	0.96, 1.07	.545
Male	5.61	0.99, 31.60	.051
Pseudo r-squared = 0.25			
Range \geq 105 mg/dL	20.35	2.33, 177.72	.006
Age	1.03	0.97, 1.09	.337
Male	7.01	1.12, 43.70	.037
Pseudo r-squared = 0.32			

N = 62; *bold numbers represent P values less than .05.

hospitalization ($P = .0003$). A glucose range greater than or equal to the median of 105 mg/dL was associated with higher odds of mortality in the model adjusted for age and male gender (Table 2). Diabetes status was dropped from the models due to multicollinearity with glucose range. The odds ratio for glucose range \geq 105 mg/dL is extremely large but reflects the substantial variation in mortality between individuals with ranges above and below that value. The mortality rate in patients with glucose range $<$ 105 mg/dL was 3.3% (N = 30); the mortality rate in patients with a glucose range \geq 105 mg/dL was 43.8% (N = 32, $t = -4.14$, $P = .001$). The mean variability in glucose levels over the first 7 days of hospitalization are illustrated in Figure 2A for patients admitted to an inpatient service and Figure 2B for patients admitted to the medical intensive care unit.

Discussion

Our results indicate that high admission glucose levels, high glucose levels during the first 7 days of hospitalization, and wide glucose ranges during the first 7 days of hospitalization are associated with increased mortality. These results suggest that patients with poor glucose control may be at

risk for poor outcomes and warrant consideration in studies on the disease course and the distribution of tissue infection in COVID-19. An admission glucose level greater than 180 mg/dL provides a single number of clinicians can use to identify high risk patients.⁶ The median value for glucose range (or variability) in our data, 105 mg/dL, is somewhat arbitrary, but it provided a clear dividing line for mortality risk, with only 1 patient with glucose range below that value dying during the study period.

Wang et al retrospectively reviewed the outcomes of COVID-19 patients admitted to 2 hospitals in China.⁷ This study included 605 patients; 114 died in the hospital. Cox regression analysis showed that age, male gender, CRB 65 scores (a clinical prediction rule for the severity of community-acquired pneumonia), and fasting blood glucose levels greater than 7 mmol/L (126 mg/dL) were independent predictors of 28-day mortality. Fasting blood sugar also predicted in-hospital complications, including acute cardiac injury, acute kidney injury, acute liver injury, cerebrovascular accident, coagulopathy, and secondary bacterial infection. This study excluded patients with a premonitory diagnosis of diabetes and included only patients who had a glucose level measured within 24 h of admission after at least an 8-h fast. Our analysis used admission nonfasting glucose levels.

Bode et al analyzed information collected by an insulin software titration company that maintains a very large database of clinical and glyceemic data in hospitalized patients.⁸ Point-of-care glucose levels are transmitted and stored for all patients on contracted hospital units. This study included 1122 patients with COVID-19, including 194 with diabetes and 257 with uncontrolled glucose levels defined by a blood glucose greater than 180 mg/dL \times 2 in a 24-h period. The admission glucose level was 202 mg/dL in this subset of patients and was 114 mg/dL in the other patients. Patients with diabetes and uncontrolled hyperglycemia had a mortality rate of 28.8% compared to a mortality rate of 6.2% in other patients. They also had an increased length of stay.

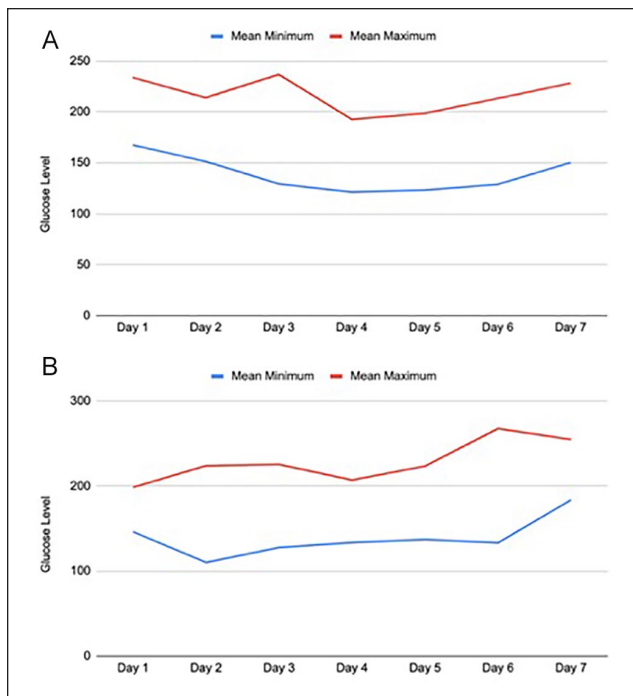


Figure 2. Plots the mean maximum and mean minimum glucose level over the first 7 days of hospitalization in patients admitted to an inpatient hospital ward (A) and patients admitted to the medical intensive care unit (B).

These results suggest that acute hyperglycemia is possibly an independent risk factor for death and suggest that management goals should aim for a glucose level of less than 180 mg/dL. Iacobellis et al analyzed the association between daily glucose levels and semi-quantitative radiographic scores ranging from 0 to 3 in patients with COVID-19.⁹ In simple regression analysis the average daily blood glucose was positively correlated with the daily radiographic score. These authors suggested that acute hyperglycemia might contribute to abnormal inflammatory and immune responses and consequently the development and progression of ARDS in these patients. The editorial associated with this article suggested that rapid blood glucose control should be mandatory in these patients.¹⁰ Although our data suggest substantially lower mortality rate in individuals with better glucose control, these individuals may have had better overall health prior to admission to the hospital. Therefore, it is unknown whether more aggressive management of hyperglycemia would directly impact survival in patients with COVID-19.

Chan and colleagues reported 6 patients who presented with diabetic ketoacidosis and hyperosmolarity with COVID-19.¹¹ The median age was 50, all patients were male, 3 patients were Hispanic, and 3 patients were African-American. The admitting glucose levels ranged from 604 to 1130 mg/dL; the admitting bicarbonate levels ranged from

less than 5 to 11 meq/L. Four patients died. Coronavirus 2 could cause direct effects on the pancreas through infection, or it could inhibit insulin secretion through down-regulation of angiotensin converting enzyme 2 activity.

Liu and colleagues reviewed bulk RNA-seq data from GTEx to determine whether or not angiotensin-converting enzyme 2 is expressed in the pancreas.¹² They found that this enzyme was expressed more in the pancreas than in the lung and that it was present in both exocrine glands and islets. Consequently, it is reasonable to think that the coronavirus 2 can infect the pancreatic cells and could cause significant injury and reduce insulin production. Yang identified ACE2 receptor staining in the lung, heart, kidney, and islets of pancreas in patients who died during the SARS epidemic.¹³ Wang et al reported that 9 of patients out of 52 patients with COVID-19 pneumonia had a pancreatic injury.¹⁴ These patients have a higher incidence of anorexia and diarrhea. Lipase level range from 45 to 124 U/L; amylase level ranged from 84 to 149 U/L. Six of the patients had abnormal glucose levels. These results suggest that the virus can directly infect the pancreas. Alternatively, they could reflect nonspecific inflammatory responses in the pancreas associated with severe illness.

Glucose Effects

Acute hyperglycemia can have important metabolic effects. High glucose levels lead to an osmotic diuresis with electrolyte loss and hypovolemia and can inhibit host defenses.¹⁵ Hyperglycemia stimulates the synthesis of advanced glycation end products which in turn bind to proteins, lipids, and cellular membranes.¹⁶ Binding to cellular membranes could lead to endothelial dysfunction. Fluctuations in glucose levels in vivo using glucose clamp methods increase oxidative stress and endothelial dysfunction.¹⁷ These effects could explain the association between glucose levels and radiographic infiltrates reported in the study by Iacobellis et al.⁹ Studies on the adverse outcomes associated with hyperglycemia have analyzed admission glucose levels, peak glucose levels during hospitalization, glucose variability during hospitalization, and the percent of glucose levels in a given target range.¹⁸ Large databases with COVID-19 patients have the potential to study many of these associations.

Limitations

This study involved a relatively small number of patients admitted to 1 hospital. A prior diagnosis of diabetes was identified through medical record review, and hemoglobin A1c levels were not obtained. Patients on non-ICU hospital services were managed by multiple physicians, and there was no standard protocol for the management of hyperglycemia. Patients who died soon after hospitalization had potentially fewer glucose readings to calculate their ranges,

and this could bias comparison to glucose ranges in those who survived. However, given that ranges were significantly higher in patients who died, this possible bias did not seem to have a substantial effect.

Conclusion

Glucose levels are readily available laboratory tests which have important clinical implications in patients with COVID-19. In our cohort of patients with COVID-19, high glucose levels appear to represent a risk factor for mortality. High glucose levels also indicate the need for more studies on the pathogenesis of pancreatic dysfunction and on insulin levels in patients with this viral infection. It is unknown whether more stringent glucose control would contribute to better survival in COVID-19 patients, but this study highlights that individuals with hyperglycemia at admission and wide glucose range during hospitalization may be at increased risk for poor outcomes with COVID-19. Management protocols to keep glucose levels in a “safer” range, possibly 140 to 180 mg/dL, might improve outcomes.⁶

Declaration of Conflicting Interests

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