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EATING AND GLYCEMIC CONTROL AMONG CRITICALLY ILL PATIENTS RECEIVING CONTINUOUS INTRAVENOUS INSULIN

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Abstract

Objective: Consensus guidelines recommend that intensive care unit (ICU) patients with blood glucose (BG) levels >180 mg/dL receive continuous IV insulin (CII). The effectiveness of CII at controlling BG levels among patients who are eating relative to those who are not eating (NPO) has not been described.

Methods: We conducted a retrospective cohort study of 260 adult patients (156 ever eating, 104 NPO) admitted to an ICU between 1/1/2014–12/31/2014 who received CII. Patients were excluded for a diagnosis of diabetic ketoacidosis or hyperglycemic hyperosmolar nonketotic syndrome, admission to an obstetrics service, or receiving continuous enteral or parenteral nutrition.

Results: Among 22 baseline characteristics, the proportion of patients receiving glucocorticoid treatment (GCTx) (17.3% Eating, 37.5% NPO, $p<0.001$) and APACHE II score (15.0 ± 7.5 Eating, 17.9 ± 7.9 NPO, $p=0.004$) were significantly different between eating and NPO patients. There was no significant difference in the primary outcome of patient-day weighted mean BG overall (153 ± 8 mg/dL Eating, 156 ± 7 mg/dL NPO, $p=0.73$) or day-by-day ($p=0.37$) adjusted for GCTx and APACHE score. Surprisingly, there was a significant difference in the distribution of BG values, with eating patients having a higher percentage of BG readings in the recommended range of 140–180 mg/dL. However, eating patients showed greater glucose variability (coefficient of variation 23.1 ± 1.0 Eating, 21.2 ± 1.0 NPO, $p=0.034$).

Conclusions: Eating may not adversely affect BG levels of ICU patients receiving CII. Whether or not prandial insulin improves glycemic control in this setting should be studied.

Hyperglycemia is a commonly encountered metabolic derangement in Intensive Care Units (ICUs), affecting up to 80% of patients.^{1,2} Both hyperglycemia and hypoglycemia are associated with adverse clinical outcomes such as critical-illness polyneuropathy, prolonged

mechanical ventilation, and mortality,^{3,4} suggesting the importance of avoiding extreme blood glucose levels in critically ill patients. Consensus guidelines from the American Diabetes Association and the American Association of Clinical Endocrinologists recommend that ICU patients with blood glucose levels persistently above 180 mg/dL be given continuous intravenous (IV) insulin infusion (CII) to maintain levels between 140 and 180 mg/dL.⁵ Furthermore, observational studies have shown that glycemic variability is a strong independent risk factor for mortality in critically ill patients.^{6,7} As a result, current critical care guidelines suggest reducing glycemic variability in addition to avoiding extreme blood glucose levels.⁸

Very little is known about the impact of eating on glycemic control in ICU patients receiving CII. Although most ICU patients are not eating, some patients do receive oral nutrition, especially as they recover. Maintaining blood glucose levels in the target range can be challenging among patients who are eating, because CII without specific meal-time (prandial) insulin delivery may not prevent post-meal blood glucose elevations. Furthermore, because CII is adjusted hourly but blood glucose levels may change more rapidly,⁹ patients may be over-treated with insulin in response to post-meal hyperglycemia and subsequently develop iatrogenic hypoglycemia. Although these phenomena have been reported anecdotally, to our knowledge a systematic description has not been published. It is possible that prandial insulin may minimize these effects. To better understand whether such additional treatments may be warranted, it is necessary to describe the effect of eating on blood glucose levels of critically-ill patients receiving CII.

We performed a retrospective cohort study of ICU patients to investigate the relationship between eating and glycemic control during CII therapy. Patients receiving CII who are eating were hypothesized to have higher patient-day-weighted mean blood glucose levels, higher rates of hyperglycemia and hypoglycemia, and greater glycemic variability than patients who are not eating.

RESEARCH DESIGN AND METHODS

Study sample:

Abstracting data from the electronic medical record (Eclipsys-Desktop 7000) as well as scanned paper charts, we conducted a retrospective cohort study of patients admitted to one of several ICUs (medical, respiratory, cardiac, surgical, neurologic or burn) between 1/1/2014 and 12/31/2014 at Temple University Hospital, an urban academic medical center. This time frame was chosen as the most recent time period before prandial insulin was added to the insulin protocol. Based on pharmacy orders, we identified patients who received CII during that time. Patients were excluded for diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome during the hospitalization, age less than 18 years, admission to an obstetric service (indicating pregnancy), or receiving continuous enteral feeds or total parenteral nutrition. Eating status was evaluated each day that CII delivery was documented. Patients with an active oral diet order were presumed to be eating on a given day. Notes from nursing staff and dietary staff were used to estimate amount of food intake (percentage of tray eaten) among the subset of patients for whom the notes were documented. Patients with a null per os (NPO) order and those without a diet order were

presumed to be not eating (NPO). Data were collected for up to 7 days on CII. If 2 glucose values were obtained within 5 minutes of each other, the first value was discarded. Patients received CII based on the Yale Insulin Infusion Protocol for critically ill patients.¹⁰ Of note, the protocol targets a BG level of 120–160 mg/dL and provided a median BG of 150 mg/dL after the target was reached in a prior study.¹⁰ Our version of the Yale protocol during the study period was executed from a paper version and stated that once patients were stable with three consecutive values in target range, the frequency of blood glucose testing is reduced to every 2 hours (See appendix). Patients who received pre-meal IV or subcutaneous insulin were excluded from the analysis. Days without any CII delivery documented were excluded from analysis.

A total of 22 baseline characteristics and potential confounders were collected as follows: age on the date of hospital admission, sex, race, ethnicity, body mass index (BMI), history of diabetes, surgery during hospital stay, sepsis, glucocorticoid treatment, hemoglobin A1c (HbA1c), serum laboratory values (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, white blood cell count, hemoglobin, hematocrit, platelet count), and APACHE II score.¹¹ All serum chemistry measurements were based upon the first measurement during the ICU stay. If HbA1c was not tested during the hospital stay, then the most recent value prior to admission was used. Surgery was defined as a procedure done in an operating room by a surgical team. Diabetes history was based upon chart review and expert adjudication by one of the authors, an endocrinologist (DR).

The primary outcome was patient-day-weighted mean blood glucose level (PDWMBG).¹² Secondary outcomes were 1) average blood glucose per hour on CII day two, the time when the most patients received CII for the most hours, 2) percentage of all blood glucose measurements in the recommended range of 140–180 mg/dL, 3) percentage of all hypoglycemic measurements per group (glucose <70 mg/dL), 4) percentage of all hyperglycemic measurements per group (glucose >180 mg/dL), and 5) glycemic variability as defined by coefficient of variation (CV) of all glucose values.¹³ Except for the baseline laboratory values, all glucose values were point-of-care (POC) capillary glucose measurements transcribed from flow sheets in the paper medical record.

Statistical analysis:

Baseline characteristics were compared between unmatched patients who ever ate (Ever eating) and those who never ate (NPO) during CII treatment. All other analyses were based on eating status each day, in which eating days were compared to NPO days. Summaries of categorical variables included counts and percentages, while means and standard deviations were used for continuous variables. Chi-square tests were used for categorical variables and 2-sample t-tests for continuous variables. A linear mixed effects model was used to compare PDWMBG levels between NPO and eating patient days, adjusted and not adjusted for differences in baseline characteristics. A linear mixed effects model was used to compare CV between NPO and eating patient days and adjust for confounders. PDWMBG and CV are reported as means and standard errors. A p value less than 0.05 was considered statistically significant. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). The Temple University Institutional Review Board approved the protocol.

RESULTS

Of 522 patients receiving CII during the study period, 260 (50%) met eligibility criteria and were included in the analysis. A total of 156 patients were ever eating and 104 were never eating (NPO). In the cohort, mean age was 63 years, 56% were male, 41% white, 26% black, and 19% were Hispanic (Table 1). A majority (77%) of patients had surgery during their hospital stay, 10% had sepsis and 25% received glucocorticoid treatment during their hospital stay. A total of 49% had a history of diabetes, mean BMI was 30.1 kg/m², and the mean HbA1c level was 7.2%. There were 2 statistically significant differences in baseline characteristics between ever-eating and NPO patients. Ever-eating patients were less likely than NPO patients to receive glucocorticoid treatment (17.3% vs 37.5%, $p<0.001$) and had a lower APACHE II score (15.0 $\pm$ 7.5 vs 17.9 $\pm$ 7.9, $p=0.004$).

Among eating patients, 98 (63%) were ordered a “heart healthy” diet, 36 (23%) were ordered a “diabetic diet” and 18 (12%) were ordered a clear liquid diet. The remaining 4 (3%) patients were ordered a different diet. The carbohydrate content for these specific diets was not available.

There were 2,773 blood glucose values obtained on 275 eating days and 3,739 blood glucose values obtained on 405 NPO days (10.1 BGs per eating patient-day vs. 9.2 BGs per NPO patient-day, $p<0.001$). The overall PDWMBG of eating days (147 $\pm$ 8 mg/dL) was not significantly different from the PDWMBG of NPO days (153 $\pm$ 7 mg/dL) ($p=0.56$). When adjusted for APACHE II score and glucocorticoid use, the eating days PDWMBG was 153 $\pm$ 8 mg/dL and the NPO days PDWMBG was 156 $\pm$ 7 mg/dL, which was also not a statistically significant difference ($p=0.73$). When PDWMBG was compared between eating and NPO days on a per-day basis, there remained no difference between groups (overall $p=0.37$, Figure 1). Documentation of percent of meals consumed was available for 111 (40%) of the eating days. When eating patients were stratified by the daily percent of meals consumed, there was no difference in the PDWMBG among any of the eating groups ($p=0.82$), and there was no interaction by day ($p=0.85$, Supplemental Figure 1).

On CII day two, 1,477 blood glucose values were obtained from 119 eating patients and 1,370 blood glucose values were obtained from 113 NPO patients (12.4 BGs per eating patients vs. 12.1 BGs per NPO patients, $p=0.53$). There was no significant difference in hourly average blood glucose levels ($p=0.62$) on CII day 2, nor was there a difference over time between groups ($p=0.27$, Figure 2).

In contrast to the lack of differences in overall PDWMBG, there was a statistically significant difference in the distribution of BG readings, with eating days having a higher percentage of BG readings 70–140 mg/dL and 141–180 mg/dL and a lower percentage of BG readings >180 mg/dL than NPO days ($p=0.0002$, Figure 3, non-adjusted). Patients on eating days also showed greater glucose variability as measured by CV and adjusted for APACHE II score and glucocorticoid use (23.1 $\pm$ 1.0 eating, 21.2 $\pm$ 1.0 NPO, $p=0.034$, Figure 4).

DISCUSSION

This retrospective cohort study of glucose control among ICU patients on CII demonstrated no difference in overall PDWMBG or hourly mean blood glucose between patients on eating days compared with NPO days. We did, however, find a statistically significant difference in the percentage of blood glucose readings in range that favored patients during eating days, as well as modestly greater glucose variability on eating days.

There are few published studies that have examined associations between eating and glycemic control among patients receiving CII. One study of non-ICU patients found that oral nutrition was associated with more frequent hyperglycemia compared with being NPO.¹⁴ To our knowledge, no previous study has explored the relationship between eating status and glycemia in a critical care setting.

Anecdotally, ICU patients who eat while receiving CII may experience post-prandial hyperglycemia and subsequent hypoglycemia as the CII is titrated in response to blood glucose levels. However, our data show no significant difference in mean blood glucose levels between eating and NPO patient days regardless of how much was being consumed. In fact, patients on eating days had slightly better glycemic control in terms of the proportion of glucose readings in the ranges of 70–140 and 141–180 mg/dL as well as less hyperglycemia >180 mg/dL. This finding may be more attributable to the less ill clinical status of patients who are able to eat compared to those who were NPO, as indicated by their APACHE II scores, rather than an effect of eating per se. It is also possible that there was an unmeasured difference between the two groups in how insulin was titrated. Although there were 10.1 blood glucoses per eating patient-days and 9.2 BGs per NPO patient-days, this seems unlikely to account for the difference in glucoses in range. While there was a modest and statistically significant increase in glucose variability among patients on eating days, the clinical significance of this finding is unclear. This study suggests that eating status does not substantially impact blood glucose control among critically-ill patients receiving CII. A possible implication is that additional prandial insulin may not be necessary in ICU patients eating while on CII.

Our study is limited by a number of factors. First, the study is retrospective and residual confounding cannot be ruled out. Second, findings from our single center may not apply to other institutions. Third, we relied on a diet order to classify a patient as eating because documentation of actual meal intake was limited. Misclassification of eating status may have introduced bias toward the null. Fourth, we relied on POC glucose measurements documented on flow sheets in the paper medical record transcribed manually into the research database, creating the possibility of data entry errors. However, we do not believe there was a differential in this potential error rate between eating and NPO patients, thereby making a substantial measurement bias unlikely. Fifth, although we included the distribution of the types of diets ordered, data on the calorie or carbohydrate content of meals were unavailable. Lastly, complete data on total daily insulin doses were unavailable.

These limitations are balanced by a few strengths. The cohort was well-described across 22 baseline characteristics recorded by detailed chart review. In addition, the study sample is racially and ethnically diverse and well-balanced in terms of sex and a history of diabetes.

Additional research is needed to further clarify the potential relationship between eating and glycemic control among patients receiving CII. A larger sample size and better documentation of food intake would provide more robust data. Assessing associations among eating, glycemic control, and clinical outcomes such as length of ICU or hospital stay and mortality could better inform treatment decisions. Whether or not prandial insulin improves glycemic control among ICU patients receiving CII should be specifically studied, ideally in a randomized controlled trial.

In conclusion, our data suggest that eating while on CII in a critical care setting may not adversely affect glucose control. The amount of food intake does not seem to modify this lack of effect. While eating is associated with a modest increase in glycemic variability, the clinical significance of this finding is unclear. More research is needed to better characterize any relationship between eating and glycemic control among patients receiving CII.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations:

ICU	Intensive Care Unit
IV	Intravenous
CII	continuous insulin infusion
NPO	null per os
BG	Blood Glucose
BMI	Body Mass Index
HbA1c	Hemoglobin A1c
PDWMBG	Patient Day Weighted Mean Blood Glucose
CV	Coefficient of Variation
POC	Point of Care

REFERENCES

1. Honiden S and Inzucchi SE. Metabolic Management during Critical Illness: Glycemic Control in the ICU. *Semin Respir Crit Care Med*. 2015;36:859–869. [PubMed: 26595046]
2. Plummer MP, Bellomo R, Cousins CE, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. *Intensive Care Med*. 2014; 40:973–980 [PubMed: 24760120]

3. Godinjak A, et al. Hyperglycemia in Critically Ill Patients: Management and Prognosis. *Med Arch*. 2015;69:157–160 [PubMed: 26261382]
4. Finfer S, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med*. 2012; 367:1108–1118. [PubMed: 22992074]
5. Moghissi ES, et al. American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control. *Diabetes Care*. 2009; 32:1119–1131 [PubMed: 19429873]
6. Egi M, Bellomo R, Stachowski E, et al.: Variability of blood glucose monitoring and short term mortality of critically ill patients. *Anesthesiology* 2006; 105:244–252 [PubMed: 16871057]
7. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med*. 2008;36:3008–3013 [PubMed: 18824908]
8. Jacobi J, Bircher N, Krinsley J, et al. Guideline for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med*. 2012;40:3251–3276 [PubMed: 23164767]
9. Clergeau A, Parienti J, Reznik Y, et al. Impact of a paper-based dynamic insulin infusion protocol on glycemic variability, time in target, and hypoglycemic risk: A stepped wedge trial in medical intensive care unit patients. *Diabetes Technology & Therapeutics*. 2017, 19: 115–123. [PubMed: 28118045]
10. Shetty S, Inzucchi SE, Goldberg PA, et al. Adapting to the new consensus guidelines for managing hyperglycemia during critical illness: the updated Yale insulin infusion protocol. *Endocr Pract*. 2012;18:363–370. [PubMed: 22138078]
11. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818–829. [PubMed: 3928249]
12. Munoz M, et al. Implementing and Evaluating a Multicomponent Inpatient Diabetes Management Program: Putting Research into Practice. *Jt Comm J Qual Patient Saf*. 2012; 38:195–206. [PubMed: 22649859]
13. Monnier L, Colette C, Owens DR. Glycemic variability: the third component of the dysglycemia in diabetes. Is it important? How to measure it? *J Diabetes Sci Technol*. 2008; 2:1094–1100. [PubMed: 19885298]
14. Smiley D, Rhee M, Peng L, Roediger L, Mulligan P, Satterwhite L, Bowen P and Umpierrez GE. Safety and efficacy of continuous insulin infusion in noncritical care settings. *J Hosp Med*. 2010;5:212–217 [PubMed: 20394026]

Figure 1. Patient-day-weighted mean blood glucose per day.

The number of patient days analyzed each day of CII is noted below the x-axis. There was no difference in PDWMBG per day between eating days and NPO days ($p = 0.37$).

Figure 2. Continuous insulin infusion day 2 glucose variation with time.

There was no difference in average blood glucose levels between eating and NPO patients ($p=0.62$), nor was there a difference in average blood glucose levels between these groups over time ($p=0.27$).

Figure 3. Blood glucose control in eating vs. NPO patients.

There was a significant difference in the overall distribution of point of care (POC) blood glucose readings between eating days and NPO days ($p=0.0002$).

Figure 4. Blood glucose coefficient of variation by day.

The number of patient days analyzed each day of CII is the same as in Figure 1. There was significantly higher variability of blood glucose readings among the eating days compared to NPO days ($p=0.034$).

Table 1–

Baseline characteristics of ICU patients receiving continuous intravenous insulin

Variable	Total Population	Ever eating	Not eating	P value
n	260	156	104	
Age on date of admission (years)	62.9 +/- 13.1	63.4 +/- 13.6	62.1 +/- 12.5	0.46
Sex, male	147 (56.1)	89 (56.3)	58 (55.8)	0.93
Race				0.32
White	106 (40.5)	71 (44.9)	35 (33.7)	
Black	68 (26.0)	39 (24.7)	29 (27.9)	
Unknown	19 (7.3)	10 (6.3)	9 (8.7)	
Other	69 (26.3)	38 (24.1)	31 (29.8)	
Hispanic	49 (18.7)	24 (15.2)	25 (24.0)	0.17
Body mass index (kg/m ²)	30.1 +/- 6.8	30.1 +/- 6.9	30.1 +/- 6.7	0.96
Diabetes	127 (48.5)	80 (50.6)	47 (45.2)	0.39
Surgery during hospital stay	201 (76.7)	124 (78.5)	77 (74.0)	0.41
Sepsis	27 (10.3)	13 (8.2)	14 (13.5)	0.17
Glucocorticoid treatment	67 (25.6)	28 (17.7)	39 (37.5)	<0.001
Lab Values				
Hemoglobin A1c (%)	7.2 +/- 2.1	7.2 +/- 2.1	7.2 +/- 2.1	0.82
Sodium (mmol/L)	138 +/- 4.7	137 +/- 4.6	137 +/- 4.8	0.90
Potassium (mmol/L)	4.2 +/- 0.8	4.2 +/- 0.7	4.2 +/- 1.0	0.89
Chloride (mmol/L)	104 +/- 6.6	104 +/- 5.8	103 +/- 7.6	0.16
Bicarbonate (mmol/L)	23 +/- 5.7	23 +/- 4.3	23 +/- 7.3	0.95
Blood urea nitrogen (mg/dL)	25 +/- 23	24 +/- 22	27 +/- 23	0.37
Creatinine (mg/dL)	1.65 +/- 1.75	1.52 +/- 1.45	1.85 +/- 2.11	0.18
Blood glucose (mg/dL)	201 +/- 136	191 +/- 117	216 +/- 160	0.16
White blood cells (K/mm ³)	13.4 +/- 8.0	13.5 +/- 8.6	13.2 +/- 7.2	0.78
Hemoglobin (g/dL)	11.5 +/- 2.3	11.5 +/- 2.2	11.6 +/- 2.4	0.93
Hematocrit (%)	34.8 +/- 6.98	34.7 +/- 6.5	34.9 +/- 7.5	0.85
Platelet count (K/mm ³)	198 +/- 101	191 +/- 92	210 +/- 113	0.15
Apache II Score	16.2 +/- 7.7	15.0 +/- 7.5	17.9 +/- 7.9	0.004

Values are n (%) or mean +/- standard deviation