Original Article

The association between glucose levels and hospital outcomes in patients with acute exacerbations of chronic obstructive pulmonary disease

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Abstract:

BACKGROUND: Corticosteroids used for chronic obstructive pulmonary disease (COPD) exacerbations can cause hyperglycemia in hospitalized patients, and hyperglycemia may be associated with increased mortality, length of stay (LOS), and re-admissions in these patients.

METHODS: We did three retrospective studies using charts from July 2008 through June 2009, January 2006 through December 2010, and October 2010 through March 2011. We collected demographic and clinical information, laboratory results, radiographic results, and information on LOS, mortality, and re-admission.

RESULTS: Glucose levels did not predict outcomes in any of the studied cohorts, after adjustment for covariates in multivariable analysis. The first database included 30 patients admitted to non-intensive care unit (ICU) hospital beds. Six of 20 non-diabetic patients had peak glucoses above 200 mg/dl. Nine of the ten diabetic patients had peak glucoses above 200 mg/dl. The maximum daily corticosteroid dose had no apparent effect on the glucose levels. The second database included 217 patients admitted to ICUs. The initial blood glucose was higher in patients who died than those who survived using bivariate analysis ($P = 0.015$; odds ratio, OR, 1.01) but not in multivariable analysis. Multivariable logistic regression analysis also demonstrated that glucose levels did not affect LOS. The third database analyzing COPD re-admission rates included 81 patients; the peak glucose levels were not associated with re-admission.

CONCLUSIONS: Our data demonstrate that COPD patients treated with corticosteroids developed significant hyperglycemia, but the increase in blood glucose levels did not correlate with the maximum dose of corticosteroids. Blood glucose levels were not associated with mortality, LOS, or re-admission rates.

Key words:

Acute exacerbation, adverse effects, complications, COPD, corticosteroids, hyperglycemia, outcomes

Chronic obstructive pulmonary disease (COPD) has significant adverse effects on quality of life and life expectancy. According to the World Health Organization (WHO) website, COPD was the fifth leading cause of death in 2002, total deaths will increase by more than 30% over the next 10 years, and by 2030, COPD will be the third leading cause of death worldwide.[1] Patients with COPD often have acute exacerbations (AECOPD) which require hospitalization, and these hospitalized patients have higher mortality rates and costs than patients managed as outpatients. Hospital mortality has been associated with some clinical parameters, such as a low Glasgow Coma Scale score, cardiorespiratory arrest prior to admission, and higher acute physiology scores.[2] A cochrane database systematic review found that patients given corticosteroids had significantly fewer treatment failures within 30 days. Hospital stays were shorter, and lung function and dyspnea improved. However, adverse events, including hyperglycemia, were more frequent.[3] Hyperglycemia has been associated with adverse clinical outcomes in patients with AECOPD in several studies.[4] Baker reported that hyperglycemia was associated with an increased relative risk of death or longer inpatient stay and that a 1 mmol/L (18 mg/dl) increase in blood glucose increased the risk of adverse outcomes by 15%.[4] The authors also reported more frequent isolation of multiple pathogens and *Staphylococcus aureus* from sputum of patients with higher blood glucose levels. Hyperglycemia has been associated with poor outcomes in several medical disorders, including stroke, myocardial infarction, and pneumonia.[5-7] We have reviewed the associations between glucose levels and corticosteroid dosage, between initial glucose levels and length of stay (LOS) and mortality, and between peak glucose levels and re-admission in three separate cohorts of patients hospitalized for acute exacerbations of COPD. We thought this approach could help

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us understand the relationships between glucose levels and management strategies and key outcomes.

Methods

The information reported in this manuscript was collected during three separate projects in the same hospital. The first cohort included COPD patients admitted for an acute exacerbation to a non-ICU bed to determine if there was a relationship between corticosteroid dosage and hyperglycemia. The second cohort included COPD patients with acute exacerbations who were admitted to the MICU to determine factors associated with mortality and LOS. The third cohort included COPD patients who were monitored for re-admission within 30 days after discharge for an acute exacerbation. The Texas Tech University Health Sciences Center Lubbock/Odessa Institutional Review Board approved these studies.

Cohort # 1: Glucose levels and corticosteroid dosage

We did a retrospective study at University Medical Center in Lubbock, TX, using charts from July 1, 2008 through June 30, 2009. These charts were identified by the billing office in the Department of Internal Medicine. We included all adult patients with a discharge diagnosis of COPD exacerbation identified by the coders in the Department of Internal Medicine; we excluded patients younger than 18 years and those admitted to an ICU. Data collected included forced expiratory volume in 1 second (FEV1), history of diabetes, blood glucose at admission, peak glucose, and maximum daily dose of corticosteroid.

Cohort #2: Glucose levels and mortality and LOS

We retrospectively reviewed charts of patients at University Medical Center in Lubbock, TX, diagnosed with COPD exacerbations who needed ICU admission. The medical records department used ICD 9 codes 491.21 to identify patients admitted between January 1, 2006 and December 31, 2010. The inclusion criteria were age 45 years or older, a diagnosis with COPD exacerbation defined by at least two criteria (increased dyspnea, cough increased in frequency and severity, and sputum production increased in volume and/or changed character), and admission to the ICU. The exclusion criteria included a history of another respiratory disease, such as asthma, or a cardiac disorder resulting in congestive heart failure which caused the acute respiratory distress.

Data collected included the patients' ages, sex, body mass indices (BMI), baseline pulmonary function tests, comorbidities, complete blood counts (CBCs), complete metabolic profiles, albumin levels, initial arterial blood gases, sputum cultures, blood cultures, chest X-rays, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, confusion, urea, respiratory rate, systolic blood pressure (CURB65) scores, final diagnoses, total duration of hospital stay, and in-hospital mortality. We separated patients into two groups: Group One died during hospitalization and Group Two survived to hospital discharge. The primary outcome in this study was the identification factors associated with increased in-hospital mortality; the secondary outcome was the identification of the factors associated with increased LOS. We separated patients by LOS into four quartiles to identify parameters associated with increased LOS.[8,9]

Cohort # 3: Peak glucose levels and re-admission

We retrospectively reviewed COPD patients who were admitted to University Medical Center in Lubbock, TX, between October 1, 2010 and March 31, 2011 and then re-admitted within 30 days. The medical record numbers were available from the University Medical Center (UMC) case management office which was collecting information on these Centers for Medicare and Medicaid Services performance measure. From electronic medical records and case management resources, we collected the highest blood glucose level during the hospital stay for each patient and other clinical parameters which might be associated with re-admissions.[10]

Data analysis

We used descriptive statistics to summarize base line characteristics of patients in all three cohorts. T-tests and Chi square tests were used to analyze differences between patients who died and patients who survived the acute flare. Multivariable logistic regression models were used to determine factors that predicted increased mortality and LOS. T-tests were used to compare highest blood glucose levels in the early re-hospitalization group with the non-early re-hospitalization group. We then used logistic regression analysis to analyze which factors affected the early re-hospitalization rate. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 16.0; *P* - values <0.05 were consider statistically significant.

Results

The basic clinical characteristics for the three cohorts are summarized in Table 1.

Cohort #1: Glucose levels and corticosteroid dosage in non-ICU patients

Twenty non-diabetic patients had a mean initial glucose of 122 ± 33 mg/dl with a range of 83 to 238 mg/dl [Table 2]. Six patients had maximum glucose levels above 200 mg/dl. Ten patients with diabetes (DM) had mean initial glucose levels of 196 ± 110 mg/dl with a range of 77 to 446 mg/dl, and nine had maximum glucose levels above 200 mg/dl. We stratified the patients into tertiles based on the maximum daily dose of corticosteroids received during hospitalization [Table 3]. There were no differences in the initial or maximum glucose levels in these three groups ($P > 0.05$ by analysis of variance, ANOVA).

Table 1: Clinical characteristics of three cohorts

Characteristic	Cohort 1	Cohort 2	Cohort 3
Number patients	30	217	103*
Male gender, %	20	47	48
Age, years	70	67	74
FEV1, % predicted	47	42	<30***
Number with diabetes (%)	10 (33)	62 (29)	NR
Initial glucose (mg/dl)	122 (196)**	156	NR
Peak glucose (mg/dl)	184 (433)**	NR	212
Mortality (%)	NR	12	4
LOS (days)	NR	9	5
Re-admission (%)	NR	NR	13

*Total number of admissions, NR = not recorded in database, **Patients with diabetes; ***Median less than 30 % predicted, see Table 6, FEV1 = Forced expiratory volume in 1 second, LOS = length of stay

Cohort #2: Glucose levels and mortality in AECOPD patients requiring ICU admission

We identified 325 patients admitted between January 1, 2005 and January 1, 2011 to intensive care units with the ICD 9 code for AECOPD. However, after chart reviews 108 cases were excluded from the study (5 deaths, 103 survivors) because they did not meet inclusion criteria or met exclusion criteria. The majority of excluded patients had congestive heart failure with exacerbation or acute asthma and did not have an AECOPD as the primary diagnosis. Therefore, this study enrolled 217 cases with AECOPD who needed ICU admission; 26 died during hospitalization and 191 survived to hospital discharge. Eighty-nine percent of the patients who died in the hospital had a FEV1 less than 50% of predicted; 68% of the survivors had a FEV1 less than 50 % of predicted. The mean initial blood glucose on admission in this cohort was 156 ± 74.3 mg/dl (range 60 to 485 mg/dL). Univariate logistic regression analysis identified a statistically significant association between initial glucose and mortality (OR = 1.01; 95%CI: 1.001-1.01, $P = 0.015$). Multivariable logistic regression including statistically significant mortality risk factors from univariate logistic regression showed that patients who lived in a nursing home (OR 50.02; 95% CI: 2.7-923.19), had a low hemoglobin (OR 0.40; 95% CI: 0.17-0.94), were intubated (OR 27.54; 95%1.78-425.39), and had a high APACHE II score (OR 1.55; 95% CI: 1.07-2.23) were at increased risk for mortality, but the initial glucose levels were not associated with increased risk [Table 4].[8]

Table 2: Glucose levels in patients with chronic obstructive pulmonary disease often have acute exacerbations (AECOPD)

Glucose level	Non-diabetic patients ($n = 20$)	Diabetic patients ($n = 10$)
Mean initial glucose (mg/dL)	122±33*	196±110
Mean peak glucose (mg/dL)	184±55	344±117**
Mean change in glucose (mg/dL)	62±58	148±115**

*mg/dl, **$P < 0.05$, mean change in glucose is the peak level minus the initial level

Table 3: Glucose levels and maximum corticosteroid dose

Tertile of corticosteroid dose (methylprednisolone)	Initial glucose	Peak glucose
1st (0-80 mg daily)	171±114*	220±129
2nd (120-220 mg daily)	144±65	254±122
3rd (280-500 mg daily)	121±26	229±89

*mg/dl, all corticosteroid doses were converted in methylprednisolone equivalents

Cohort #2: Initial glucose levels and LOS in AECOPD patients requiring ICU admission

The overall LOS was 9.01 ± 6.00 days. It was 8.37 ± 4.99 days in survivors and 13.69 ± 9.78 days in non-survivors. Based on LOS, we separated patients into quartiles: The first quartile LOS: 1-4 days ($n = 44$), the second quartile LOS: 5-6 days ($n = 53$), the third quartile LOS: 6-10 days ($n = 58$), and the fourth quartile LOS: 11-33 days ($n = 62$). Initial mean blood glucose was 156 ± 74.3 mg/dl and did not predict a statistically significant increased LOS in univariate logistic regression analysis (OR 1.00; 95% CI: 0.99-1.01, $P = 0.59$). Univariate analysis did demonstrate that nursing home status, low albumin, the presence of a pleural effusion, intubation, and high APACHE II scores were associated with increased LOS ($P < 0.05$ for each factor). A multivariable logistic regression model demonstrated that only intubation (OR 5.93; 95%CI 2.78-12.65) predicted a statistically significant increase in hospital LOS [Table 5].[9]

Cohort # 3: Peak glucose levels and re-admission in patients with AECOPD

These patients had 103 admissions, including 13 early re-hospitalizations (12.6 %), defined as a re-hospitalization within 30 days after discharge. The mean peak blood glucose levels were 212 ± 105mg/dl with a range from 94mg/dl to 600 mg/dl. There were no differences in mean peak glucose levels between early re-hospitalization and non-early re-hospitalization patients ($P = 0.318$). The characteristics of these two groups are reported in Table 6. Multivariable logistic regression analysis showed that only the presence of unilateral pulmonary infiltration on admission (OR 5.14 [0.86-30.86], $P = 0.074$) and an ejection fraction < 55% (OR 4.57 [0.86-24.31], $P = 0.075$) possibly had an effect on early re-hospitalizations.[10]

Discussion

Our study includes information from three separate cohorts with a total of 318 COPD patients with acute exacerbations requiring hospitalization. The initial glucose levels had a wide range in the first cohort, and the mean glucose level was nearly 200 mg/dl in the patients with diabetes. Ninety percent of the patients with diabetes had a maximum glucose level during hospitalization above 200 mg/dL. There was no apparent correlation between the maximum corticosteroid

Table 4: Factors associated with mortality in patients admitted to an intensive care unit (ICU)

Factor	In hospital deaths	Survivors	*P*-value	Odds ratio	95% CI
Nursing home	15 of 26	16 of 191	0.01	50.02	2.7-923.19
Mean arterial pressure	64.1±13.4	85±18.3	0.36	0.97	0.92-1.03
Initial O2 sat	88.1±8.5	92.3±4.5	0.66	0.96	0.82-1.13
Initial blood sugar	192±97	151±69.6	0.59	1.00	0.99-1.02
Hemoglobin	11.6±2.6	13.2±2.2	0.04	0.40	0.17-0.94
Blood urea nitrogen	36.5±28.6	19±12.7	0.19	0.96	0.89-1.02
Albumin	3.1±0.7	3.7±0.5	0.19	3.87	0.52-28.85
Pleural effusion	7 of 26	15 of 181	0.07	11.22	0.80-156.92
Intubation	21 of 26 (80.7 %)	76 of 191 (39.7 %)	0.02	27.54	1.78-425.39
APACHE II score	21.9±7	11.7±4.2	0.02	1.55	1.07-2.23

Multivariable analysis, bold text represents statistically significant values at the 0.05 level or less, APACHE II = acute physiology and chronic health evaluation II

Table 5: Factors associated with length of stay in patients admitted to an intensive care unit (ICU)

Factors	*P*-value	OR (95%CI)
From nursing home	0.70	1.22 (0.44-3.35)
Initial O2 sat	0.06	0.93 (0.87-1.001)
Albumin	0.27	0.69 (0.36-1.33)
Intubation	<0.001	5.38 (2.58-11.21)
Pleural effusion	0.08	2.62 (0.89-7.74)
APACHE II	0.95	1.00 (0.94-1.07)

Multivariable analysis, bold text represents statistically significant values at a *P*-value ≤ 0.05, APACHE II = acute physiology and chronic health evaluation II

dose and the maximum glucose level in this small group of patients. The other two cohorts included patients admitted to the ICU and patients tracked for re-admission to the hospital. In the ICU cohort the initial glucose level did not predict length of stay or mortality using a multivariable model. In the cohort tracked for re-admission, the peak glucose level did not predict re-admission when used in a multivariable model. Consequently, our results demonstrate that patients with acute COPD exacerbations frequently have hyperglycemia, especially if they have diabetes, but the elevated glucose levels do not predict short-term outcomes. This does not mean that

Table 6: Comparison of patients with chronic obstructive pulmonary disease (COPD) exacerbations according to early re-hospitalization status

Characteristics	All admissions *n* = 103(%)	Early re-hospitalizations		*P* value
		Yes *n* = 13 (%)	No *n* = 90 (%)	
Ejection fraction				0.071
Unknown	29 (28.2)			
<55%	12 (11.7)	4 (30.8)	8 (8.9)	
> = 55%	62 (60.2)	7 (53.8)	55 (61.1)	
Diastolic dysfunction				
Unknown	47 (45.7)			0.537
Yes	50 (48.5)	5 (38.5)	45 (50.0)	
No	6 (5.8)	1 (7.7)	5 (5.6)	
Pulmonary artery pressure				
Unknown	46 (44.7)			0.623
Normal	22 (21.4)	1 (7.7)	21 (23.3)	
Mild PAH	15 (14.6)	1 (7.7)	14 (15.6)	
Moderate PAH	15 (14.6)	2 (15.4)	13 (14.4)	
Severe PAH	5 (4.9)	1 (7.7)	4 (4.4)	
Cor pulmonale	14 (13.6)	1 (7.7)	13 (14.4)	1.000
Beta-blocker use	35 (34.0)	4 (30.8)	31 (34.4)	1.000
Long-acting bronchodilators and/or inhaled corticosteroids	68 (66.0)	10 (76.9)	58 (64.4)	0.535
Coronary artery disease	32 (31.3)	6 (46.2)	26 (28.9)	0.217
Atrial fibrillation	11 (10.7)	0 (0)	11 (12.2)	0.351
COPD severity				
Mild (FEV1 > 80%)	1 (1.0)		1 (1.1)	0.833
Moderate (FEV1 50-79%)	8 (7.8)	0 (0)	7 (7.8)	
Severe (FEV1 30-49%)	30 (29.1)	1 (7.7)	24 (26.7)	
Very severe (FEV1 < 30%)	13 (12.6)	6 (46.2)	11 (12.2)	
PFT not done	51 (49.5)	2 (15.4)		
Unilateral infiltrate	15 (14.6)	4 (30.8)	11 (12.2)	0.204
Abnormal WBC (<4.0 or >12.0 × 10^3 /μL)	28 (27.2)	2 (15.4)	26 (28.9)	0.674
Mean blood glucose (mg %)	212	184	216	0.318
ProBNP				
<900 pg/mL	47 (45.6)	9 (69.2)	38 (42.2)	0.691
901-1800 pg/mL	9 (8.7)	1 (7.7)	8 (8.9)	
>1800 pg/mL	15 (14.6)	1 (7.7)	14 (15.6)	
ProBNP not done	32 (31.1)			
Intubation	6 (5.8)	1 (7.7)	5 (5.6)	0.565
Mean length of stay (days)	5.0	4.2	5.2	0.345
Mean follow-up (days)	16.1	20.4	15.5	0.266
Disposition				
Home	63 (61.2)	9 (69.2)	54 (60.0)	0.611
Home with HHC	11 (10.7)	0 (0)	11 (12.2)	
Inpatient facilities	25 (24.3)	4 (30.8)	21 (23.3)	
Dead	4 (3.9)			

BNP = Brain natriuretic peptide, COPD = Chronic obstructive pulmonary disease, FEV1 = Forced expiratory volume in 1 s, HHC = Home health care, PAH = Pulmonary artery hypertension, WBC = White blood cell, Bold text represents statistically significant values at a *P* - value ≤ 0.05

hyperglycemia is not consequential in some patients or when present over longer periods of time or that it does not require attention during patient management.

Glucose levels in patients with AECOPD

Baker *et al.,* measured glucose levels in 284 patients with acute exacerbations of COPD requiring hospitalization and reported the highest value measured either at admission or during the admission.[4] The median value in the entire cohort was 126 mg/dl (interquartile range (IQR): 108-162 mg/dl). Two hundred and four patients (72%) had values greater than 110 mg/dl, and 32(11%) had values greater than 200 mg/dl. The highest quartile had glucose levels greater than 162 mg/dl. Fifteen patients (5.3%) in this cohort had diabetes (DM). Parappil reviewed 246 episodes of AECOPD.[11] Forty-two percent of the admissions had a random glucose greater than 180 mg/dl, but mean values were not provided. Fifty-three patients (22%) had DM. Burt measured glucose values in 47 patients using a continuous monitoring system; the mean level was 137 ± 34 mg/dl.[12] The peak levels in their cohort were 220 ± 61 mg/dl. Seven patients (15%) had DM. Chakrabarti studied 88 patients with decompensated COPD (mean pH = 7.25) who required non-invasive ventilation.[13] Fifty percent of the patients had an admission glucose >126 mg/dl; 16 (18%) had DM. The initial glucose levels in our Cohort 2 patients were 151 mg/dl in survivors and 192 mg/dl in non-survivors; 62 patients (29%) had DM. The mean peak glucose levels ranged from 184 mg/dl in non-diabetic patients in Cohort 1 to 344 mg/dl in diabetic patients in Cohort 1. Consequently, these studies in patients with AECOPD requiring hospitalization demonstrate that peak glucose levels are variable but often high, and that 5-29% of patients with AECOPD has DM. Patients with COPD frequently have comorbid diseases, including DM, and COPD is a risk factor for the development of DM.[14,15] This association may reflect the adverse effects of medication, physical inactivity with weight gain, and possibly intermittent stress associated with acute exacerbations.

Outcomes in AECOPD patients with hyperglycemia

Several studies have evaluated the relationship between in-hospital glucose levels and AECOPD. Baker found significantly higher mortality rates and longer LOS in341 patients with acute exacerbations of COPD and increasing blood glucose levels measured during the hospitalization, independent of age, sex, and previous diagnosis of DM.[4] The absolute risk of mortality and length of hospital stay increased by 15% for each 1 mmol/L (18mg/dl) increase in blood glucose. The authors also reported more frequent isolation of multiple pathogens and *Staphylococcus aureus* from sputum of patients with increases in blood glucose. Burt reported that the mean glucose level based on continuous measurement independently predicted an increased LOS.[12] Parappil *et al.,* reported a non-significant increase in LOS and mortality in 39 patients with DM admitted with acute exacerbations of COPD.[11] However, Kasirye reported a longer LOS in patients with low glucose levels (1 daily mean value < 90 mg/dl).[16] Chakrabarti reported that hyperglycemia was associated with an increased likelihood of failure of noninvasive ventilation in 88 patients; the explanation for this association is unclear.[13] Dave reviewed outcomes in 498 patients requiring 731 admissions for acute hypercapneic respiratory failure, including 109 patients who required noninvasive ventilation.[17] Admission glucose levels were similar in patients managed on the ward and patients managed in a high dependency unit or ICU. Our studies did not identify a relationship between LOS, mortality, or re-admission. Overall, these studies report an inconsistent effect of hyperglycemia on the outcomes in patients hospitalized with COPD exacerbations. This could be explained, in part, by the glucose measurement protocols which included admission values, mean daily values, peak values, and mean continuous values. Glucose levels have a circadian pattern with higher values in the late afternoon in corticosteroid treated patients with AECOPD, and routine morning lab tests may not detect the range of glucose elevations.[18,19] In addition, glycemic variability is associated with increased length of stay and mortality in hospitalized patients and needs to be considered in these studies.[20]

Possible mechanisms for hyperglycemic effects

Patients with AECOPD frequently have hyperglycemia which could have acute adverse effects in critically ill patients through several mechanisms. High intracellular glucose concentrations increase the production of reactive oxygen species, such as superoxide, and of peroxynitrite which can impair mitochondrial function and damage proteins, cellular membranes, and nucleic acids.[21,22] Hyperglycemia causes glycosylation of proteins, impaired leukocyte function, and activation of pro-inflammatory genes through transcription factors.[21-23] Glycosuria potentially causes an osmotic diuresis with a loss of electrolytes and volume contraction which could adversely affect the clinical course. Occasionally, patients on corticosteroids develop hyperglycemic hyperosmolar syndrome or diabetic ketoacidosis. Other studies have reported that hyperglycemia increases the mortality in patients with acute myocardial infarction, with ischemic or hemorrhagic stroke, and with community-acquired pneumonia.[5-7,24]

Strengths and limitations

Our study includes a relatively large number of patients with AECOPD requiring hospitalization and considers three important outcomes. However, it does have some limitations. Medical records were identified by discharge codes, and some patients with COPD exacerbations could have been misdiagnosed with acute respiratory distress secondary to pulmonary embolus, CHF, or asthma. Some information was not consistently available in the records. Different physicians managed the patients, and different management approaches would influence the choice of medication, the dose of medication, and the frequency and type of laboratory testing. The small number of patients in our first cohort might have limited our ability to identify a statistically significant association between corticosteroid dose and hyperglycemia, but there was a very wide range of corticosteroid doses in these patients. Finally, we don't know if the development of hyperglycemia introduces practical problems in the management of the patients both in the hospital and after discharge.

In summary, our study does not identify any important associations between glucose levels and outcomes of patients with AECOPD requiring hospitalization. This conclusion seems somewhat counterintuitive but could reflect the fact that in-hospital management of hyperglycemia is relatively easy and prevents complications.[25,26] We need more information

on the frequency and severity of hyperglycemia in these patients, the factors associated with hyperglycemia, the effects of hyperglycemia on short term outcomes, and the effect of intermittent hyperglycemia on long term outcomes.

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