

# Hyperglycemia is associated with increased length of stay and total cost in patients hospitalized for congestive heart failure

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## ABSTRACT

**Objectives:** Hyperglycemia is a well-known marker of poor clinical outcomes in acute myocardial infarction and critical illness; however, its effect in congestive heart failure (CHF) is controversial. We hypothesized that persistent hyperglycemia is associated with increased length of stay (LOS) and increased total cost in patients admitted with CHF. **Methods:** We studied 203 consecutive patients admitted with a primary diagnosis of CHF. Patient characteristics, admission glucose, mean blood glucose (MBG) during the entire hospital stay, length of stay, total cost, and readmission rates were assessed. Persistent hyperglycemia was defined as a MBG level  $\geq 140$  mg/dl. **Results:** Patients with persistent hyperglycemia had longer mean LOS (8.1 vs 5.2 days,  $p = 0.001$ ) and higher total hospital costs (median \$8940 vs \$6892,  $p = 0.01$ ) independent of diabetes status. Similarly, prolonged hospital stay  $>7$  days (38% vs 21%;  $p = 0.01$ ) and total cost  $> \$10,000$ /patient (46% vs 29%;  $p = 0.01$ ) were seen more commonly in patients with poor glucometrics. Neither admission glucose  $>140$  mg/dL or diabetes status was predictive of total costs or LOS. In multivariate linear regression, only MBG  $\geq 140$  mg/dl was associated with increased LOS and total cost. Patients with persistent hyperglycemia also had higher 6 months all-cause readmission rates (51% vs 37%;  $p = 0.03$ ). **Conclusion:** Persistent hyperglycemia (MBG  $> 140$  mg/dL), but not admission glucose, was associated with increased LOS, total cost and readmission rates independent of diabetes status. Our study emphasizes the need to further examine the role of glycemic control in patients admitted with CHF.

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**Keywords:** Congestive Heart Failure; Persistent Hyperglycemia; Length of Stay; Total Cost; Diabetes; Admission Glucose

## 1. INTRODUCTION

Hyperglycemia is associated with adverse clinical outcomes in patients with acute myocardial infarction [1,2], critical illness [3-5], and coronary artery bypass grafting [6,7]. Although congestive heart failure (CHF) is by far the most common diagnosis related group requiring acute care hospitalization and is associated with high mortality rates and costs, the prognostic significance of hyperglycemia has not been well established. Similarly, limited data is available regarding the effect of hyperglycemia on costs or length of stay in CHF.

Prior data on hyperglycemia in CHF has focused predominantly on admission glucose levels [8-10]. Persistent hyperglycemia during hospitalization, however, appears to be a better predictor of CV outcomes and mortality when compared to admission glucose in the setting of acute myocardial infarction [2]. The aim of our present study was to examine the role of admission glucose and persistent hyperglycemia during hospitalization on length of stay (LOS) and total cost in patients admitted with a primary diagnosis of CHF, regardless of diabetes status. We hypothesized that persistent hyperglycemia is associated with increased with increased LOS and cost.

## 2. METHODS

We retrospectively identified a cohort of 208 consecutive patients hospitalized for dyspnea and discharged with the primary diagnosis of CHF (excluding patients with acute coronary syndromes) based on any one of the six primary

CHF ICD-9 codes (428.0, 428.1, 428.2, 428.3, 428.4, 428.9) from January through December 2008 at our university-affiliated community hospital. Detailed information on cost and length of stay, as well as readmission rates, was obtained from the information services department at our hospital after informed consent was obtained from our Institutional Review Board.

This work was previously presented at the American Heart Association scientific sessions [11].

Symptomatic patients with dyspnea were evaluated clinically, as well as biochemically and radiographically for evidence of CHF requiring admission. After extensive chart/radiographic review of each subject, five patients were excluded for an inability to confirm the diagnosis of CHF according to the Framingham criteria [12].

### 2.1. Data Source

Electronic medical records were reviewed to abstract demographic data, clinical information, including information on co-morbidities (diabetes, hypertension, coronary artery disease (CAD), chronic renal impairment), NT-Pro-BNP (N-terminal pro-brain natriuretic peptide) levels, estimated glomerular filtration rate according to the MDRD formula (eGFR, ml/min), admission glucose levels, mean blood glucose (MBG) during the entire hospitalization (including all venous and finger stick blood glucose measurements), length of stay (LOS), and total cost. Readmission to our hospital within 6 months following the index admission was also obtained. MBG was calculated by averaging all of the glucose values during entire hospitalization. Based on prior literature [2], patients were divided into two groups according to their MBG values: persistent hyperglycemia group (MBG  $\geq$  140 mg/dL) and controls (MBG < 140 mg/dL). A second cut-point of MBG > 200 mg/dl was examined separately.

### 2.2. Outcomes

The primary outcomes were length of stay and total cost. The secondary outcome was all-cause hospital readmission rate at six months following the index admission.

### 2.3. Statistical Analysis

Analysis was performed using SAS V8 software. Categorical variables, described as proportions, were compared with chi-square tests. Continuous variables were reported as medians with the inter-quartile ranges when non-normally distributed. Non-parametric variables were compared with the Wilcoxon rank sum tests. Multivariate linear and logistic regression analyses were performed to test the association between outcomes with hyperglycemia, after adjustment for effect modifiers, including

NT-Pro-BNP (log (e)), eGFR < 60 ml/min, advanced age ( $\geq$ 75 years) and race. A two tailed P-value of <0.05 was considered statistically significant. 95% two-sided confidence intervals were calculated using the exact binomial method.

## 3. RESULTS

A total of 203 patients were included in the analyses. Demographics are shown in **Table 1**. The mean age of the cohort was  $74 \pm 14$  with females comprising 44% of the total cohort. The mean blood glucose (MBG) for the entire cohort was  $137 \pm 48$  mg/dl. MBG  $\geq$ 140 mg/dl (persistent hyperglycemia) was seen in 39%. Forty nine percent of subjects were diabetic, with the majority of diabetics (70%) residing in the persistent hyperglycemia group.

In univariate analysis diabetic status, Hispanic race and patients estimated eGFR < 60 ml/min were the only factors associated with persistent hyperglycemia ( $p < 0.01$  for both). Age, gender, EF < 45%, presence of CAD and hypertension were not associated with persistent hyperglycemia. Mean NT-Pro-BNP levels was also similar between the two groups suggesting that the severity of disease was not a major factor in the development of persistent hyperglycemia.

The median cost for the entire cohort was \$7450 (range: \$1205 to \$418,815, inter-quartile range 25<sup>th</sup> - 75<sup>th</sup>: \$4979 - \$12,779). The persistent hyperglycemic group had significantly higher total cost (median \$8940 vs \$6892,  $p = 0.01$ ) than controls. Similarly, the mean total cost was greater in the persistent hyperglycemia group (\$21,924 vs \$9613;  $p = 0.01$ ). Using an arbitrary cut off of \$10,000 to define excessive cost, persistent hyperglycemia was associated with increased incidence of excessive cost (46% vs 29%, OR: 2.0: CI 1.2 - 3.7). Only MBG  $\geq$  140 mg/dl and eGFR < 60 ml/min were associated with total cost in univariate analysis. In multivariate linear regression, only MBG  $\geq$  140 mg/dl was associated with increased total cost after adjustment for NT-Pro-BNP, renal insufficiency, advanced age and Hispanic ethnicity (**Table 2**). A graded response of hyperglycemia to total cost was seen when MBG was stratified into 3 sub-groups (<140, 140 - 199, and  $\geq$ 200) (**Figure 1**).

The length of stay in the total cohort varied from 1 to 67 days, with median of 5 days (inter-quartile range 25<sup>th</sup> - 75<sup>th</sup>: 3 - 8 days). As compared to those with MBG < 140 mg/dl, patients with persistent hyperglycemia had higher mean (8.1 vs 5.2 days;  $p < 0.001$ ) and median LOS (5 vs 4 days,  $p = 0.01$ ). Using an arbitrary cutoff of 7 days as excessive LOS, the persistent hyperglycemia group was associated with an increased incidence of excessive LOS > 7 days when compared to controls (OR

**Table 1.** Demographics and clinical characteristics of the study cohort.

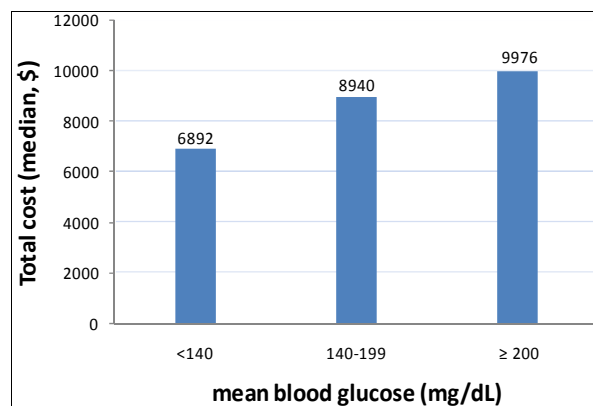
	Total cohort (N = 203)	Hyperglycemic group (MBG $\geq$ 140 mg/dl) (N = 80)	Control group (MBG < 140 mg/dl) (N = 123)	p Value
Age (mean $\pm$ SD, year)	74 $\pm$ 15	74 $\pm$ 12	74 $\pm$ 16	0.1
Gender				0.3
Male	114 (56%)	41 (51%)	73 (59%)	
Female	89 (44%)	39 (49%)	50 (41%)	
Race				<0.01
White	129	51 (54%)	78 (63%)	
Hispanic	31	20 (25%)	11 (9%)	
Black	40	7 (9%)	33 (27%)	
Others	3	2 (2%)	1 (1%)	
DM	100	70 (88%)	30 (24%)	<0.01
% on insulin	47	38 (54%)	9 (30%)	
CAD	107	45 (56%)	62 (50%)	0.4
MedianNT-Pro-BNP (25 <sup>th</sup> - 75 <sup>th</sup> )	7007 (3156 - 14,152)	7056 (3004 - 16,097)	6990 (3218 - 11,874)	0.9
EF < 45%	102	40 (50%)	62 (50%)	0.8
GFR < 60 ml/min	126	61 (76%)	65 (53%)	<0.01
HTN	179	67 (84%)	112 (91%)	0.1
Mean glucose mg/dL (mean $\pm$ SD)	137 $\pm$ 48	185 $\pm$ 41	106 $\pm$ 17	<0.01
Admission glucose mg/dl (mean $\pm$ SD)	136 $\pm$ 67	173 $\pm$ 89	112 $\pm$ 29	<0.01
Discharge glucose mg/dL (mean $\pm$ SD)	138 $\pm$ 48	173 $\pm$ 45	109 $\pm$ 25	<0.01

**Table 2.** Multivariable linear regression for total cost.

Variable	Coefficient	p Value
MBG $\geq$ 140 mg/dl	12.5	0.03
Pro-BNP (Log (e))	2.1	0.3
eGFR < 60 ml/min	3.3	0.6
Age $\geq$ 75	5.6	0.3
Hispanic	-3.3	0.7

2.2: CI 1.1 - 4.2;  $p = 0.01$ ). Only MBG  $\geq$  140 mg/dl and eGFR <60 ml/min were associated with LOS in univariate analysis. In multivariate linear regression, only MBG  $\geq$  140 mg/dl was associated with increased LOS after adjustment for NT-Pro-BNP, renal insufficiency, advanced age and Hispanic ethnicity (**Table 3**). Similarly, there was a graded response of hyperglycemia to increased LOS (**Figure 2**).

Of note, neither the presence of diabetes or admission glucose levels were associated with total cost or LOS. The readmission rate at six months was also increased in the persistent hyperglycemia group (51% vs 37%;  $p = 0.03$ ).

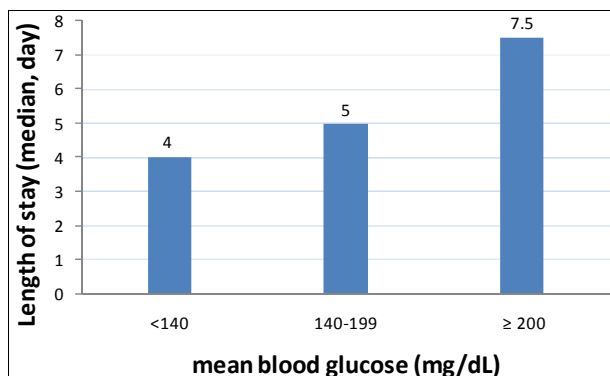
**Figure 1.** Total cost (median) among different mean blood glucose groups ( $p = 0.05$ ).

#### 4. DISCUSSION

Our study found an association between persistent hyperglycemia and increased total cost and LOS, which was independent of diabetes status and admission glucose levels. Age, median NT-Pro-BNP and left ventricular ejection were similar between the groups suggesting that increased glucose levels were not merely related to

**Table 3.** Multivariable linear regression for length of stay.

Variable	Coefficient	p Value
MBG $\geq$ 140 mg/dl	2.2	0.01
Pro-BNP (Log (e))	0.6	0.5
eGFR < 60 ml/min	0.5	0.09
Age $\geq$ 75	0.9	0.2
Hispanic	-0.3	0.8

**Figure 2.** Length of hospital stay (median) among different mean glucose groups ( $p = 0.04$ ).

the severity of CHF. One may postulate that the observed effects of hyperglycemia on LOS and total cost are likely to be related indirectly to the treatment of complications related to persistent hyperglycemia or directly at therapy aimed at improving diabetic control. Unfortunately the precise mechanism(s) can not be ascertained from this study.

The significance of hyperglycemia on morbidity and mortality in CHF remains controversial. Initial data suggested that hyperglycemia was associated with poor CHF outcomes [8-10]. In a large-scale prospective cohort study fasting plasma glucose was an independent predictor of hospitalization for CHF in high-risk subjects [13]. Similarly, blood glucose levels were associated with increased all-cause mortality in patients with CHF after hospitalization in two moderate-scale cohort studies [9,14]. However, a recent report, which evaluated a nationally representative cohort of 50,532 elderly patients hospitalized with CHF, found no significant association between admission glucose levels and either 30-day or 1-year mortality [10]. Prior studies not only yielded contradictory results, in one study only diabetic subjects were included for analysis [15]. The above studies of hyperglycemia and CHF focused primarily on mortality utilizing admission glucose values and did not assess LOS or costs associated with hospitalization for CHF. There is only limited data that focuses on length of stay [16], which is an important aspect of the overall burden

of CHF to the healthcare system, but no prior data is available to our knowledge regarding true cost.

In a prospective cohort study of 212 patients with heart failure exacerbation [16] diabetes was associated with prolonged hospital stay in CHF. Within the diabetic subgroup, both admission glucose and in-patient poor glycemic control were associated with increased LOS, but the non-diabetic cohort was not studied. Our study findings differ in showing a significant association between persistent hyperglycemia and LOS which is independent of diabetes status and admission glucose levels. Additionally, we present data on total cost and readmission rates which appear to be independent of markers of disease severity. As hyperglycemia is observed in nearly half of all patients admitted for CHF [10], the role of hyperglycemia, as well as intensive glucose lowering, warrants future study.

Hyperglycemia is known to have deleterious effects on the cardiovascular system. Hyperglycemia impairs coronary micro-circulatory responses to ischemia, reduces the availability of nitric oxide, attenuates the endothelium-dependent vascular responses, and enhances the production of oxygen derived free radicals [15]. CHF is an insulin-resistant state which is frequently exacerbated by an activation of the renin-angiotensin-sympathetic nervous system axis, as well as an increase in counter-regulatory hormones in the decompensated state. Hyperglycemia may, therefore, not simply be related to the severity of illness of CHF.

## 5. STUDY LIMITATIONS

We acknowledge multiple limitations to our study including its retrospective nature, lack of blinding, modest sample size and data limited to a single center. As hyperglycemia itself may have been the reason that physicians kept patients in longer, a causal relationship between hyperglycemia, LOS and cost can not be ascertained. However, as the persistent hyperglycemia and control groups were similar with regard to age, gender, coronary artery disease status, resting ejection fraction and NT-Pro-BNP levels, hyperglycemia does not appear to be simply a marker of disease severity. As glucose lowering was at the discretion of the physician, no conclusions can be made regarding individual glucose lowering regimens.

In conclusion, persistent hyperglycemia is associated with increased LOS, total cost and 6 month readmission rates, independent of diabetes status or admission blood glucose. Whether persistent hyperglycemia is a marker or cause for increased LOS and total cost can not be definitively ascertained in this study. Treatment targeted to hyperglycemia itself may be responsible for increased LOS and cost. Whether control of hyperglycemia during an admission for CHF will result in improved LOS or

cost is unknown. Future prospective studies examining glucometrics, as well as the role of glycemic control in reducing healthcare costs in patients with CHF are warranted.

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