

Blood glucose level and outcomes in COPD Exacerbations

Sanjay Tandon^{1*}, Deep Pawar², S.T. Nagdeote¹¹Professor, Department of Pulmonary Medicine, People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh, India²Junior Resident, Department of Pulmonary Medicine, People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh, India

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Abstract

Introduction: Hyperglycemia is associated with acute exacerbation of COPD (AECOPD) and is associated with poor outcome. Thus present study was carried out with an aim to determine the association of blood glucose level on the outcome of patients with Acute Exacerbation of COPD. **Methodology:** This was a prospective observational study conducted on hundred patients admitted with the diagnosis of AECOPD at a tertiary care hospital in central India from December 2018 and May 2020. Patients were grouped on the basis of mean capillary glucose level into four quartiles: Group A <110 mg/dl; Group B 110-125 mg/dl; Group C >125-160 mg/dl; Group D >160 mg/dl. Severity of AECOPD was assessed in each of the four quartiles. Diabetics were excluded. Data was analysed using SPSS 25 and chi square test was applied to know the statistical significance. **Results:** A positive correlation of mean blood glucose level was seen with increasing severity of AECOPD ($r=0.402$; $p=0.001$). Majority of the patients with blood glucose greater than 160 mg/dl had severe (75%) to life threatening exacerbation episodes (12.5%). The association between mean blood glucose level and LOHS was statistically significant ($p<0.001$). Patients with mean blood glucose level 126 to 160 mg/dl and >160 mg/dl had significantly longer LOHS of greater than 9 days in 67.4% and 87.5% respectively. Gram negative bacilli (34% and 25%) were isolated two times more frequently than gram positive bacteria at higher mean blood glucose level ($p<0.001$). Higher mean blood glucose level (>126 mg/dl), as opposed to lower mean blood glucose level (< 126 mg/dl), was more likely to be associated with bacterial infection as a cause of COPD exacerbation. **Conclusion:** Short term hyperglycaemia during hospital stay, in the absence of pre-existing diabetes, can have adverse outcomes in AECOPD. Higher mean blood glucose level was associated with adverse outcome with respect to severity of exacerbation of COPD, LOHS and higher rate of bacterial exacerbations. However, no association was found between increased mean blood glucose and 30 day hospital readmission and mortality.

Keywords : AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease, LOHS, blood glucose level.

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Introduction

Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is a major cause of chronic morbidity and mortality throughout the world. Patients with COPD often have acute exacerbations, which result in high resource utilization. Hence, it is a disease of increasing public health importance. Elevated blood glucose level is a well-recognised pathophysiological response to acute illness. The underlying mechanisms include acute increase in hepatic glucose production and peripheral insulin resistance driven by increase in glucocorticoids, catecholamines and pro-inflammatory cytokines. Moreover, infection (a potential cause of AECOPD) can lead to hyperglycaemia as a result of peripheral insulin resistance and alterations in hepatic glucose metabolism, leading to the overproduction of glucose [1-3]. In previous studies the outcomes of COPD exacerbation were found to be largely predicted by factors such as older age, male sex, co-morbidity, higher income and arterial pH. However, the relationship between blood glucose levels and clinical outcomes in AECOPD has not yet been fully established. Hence, the present study was performed to determine the relationship between blood glucose level and clinical outcomes in patients admitted with AECOPD [4,5].

*Correspondence

Dr. Sanjay Tandon

Professor, Department of Pulmonary Medicine, People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh, India.

E-mail: pulmedph@gmail.com

Material and methods

This was a prospective observational study with a sample size of hundred. This study was conducted over a period of one and half year between December 2018 and May 2020 at a tertiary care hospital in central India. Clearance was obtained from the Institutional Ethical Committee. A total of 124 COPD patients aged 40 years and above, presenting to the Pulmonary Medicine department, and fulfilling the AECOPD diagnostic criteria according to GOLD [1] were evaluated. Thirteen patients were excluded, as they refused blood glucose testing. Seven patients who were not expectorating and four known diabetics were also excluded. The Inclusion criteria for the study group were 1. Pre-diagnosed admitted COPD patients aged > 40 years presenting in acute exacerbation; 2. Admitted patients aged > 40 years and newly diagnosed with AECOPD; 3. Admitted patients who gave informed consent for the study. The Exclusion criteria were 1. Patients of AECOPD with myocardial infarction or Cerebrovascular accident or those requiring surgery; 2. Patients with Bronchial Asthma, Bronchiectasis, or Interstitial lung disease; 3. Patients with Diabetes mellitus; 4. Patients who did not give consent. Age, gender, smoking history, place of residence, whether rural or urban, and literacy were noted at the time of admission. According to GOLD guidelines 2018, as part of management of COPD, a short course of oral steroid was given for the first 5 days. Mean capillary blood glucose level was calculated for the first five days of hospitalization. For the ease of the study and to limit discrepancies, over the first five days of hospitalization, portable Glucometer readings were taken immediately after

admission and three times daily thereafter: Before Breakfast (BBF), two hours After Lunch (AL) and two hours After dinner (AD). For each patient, mean blood glucose value was calculated from all measurements done for five days and expressed in milligrams per decilitre. Patients were grouped into four quartiles based on their

mean blood glucose level: Group A < 110 mg/dl; Group B 110-125 mg/dl; Group C > 125-160 mg/dl; Group D > 160 mg/dl; Severity of exacerbation was determined using the Burge et, al. AECOPD severity scale[6]

Table 1: Scale for AECOPD exacerbation severity

Exacerbation severity	Criteria for Exacerbation severity
Mild:	An exacerbation treated with antibiotics but no systemic corticosteroid. If no blood gases are available, the absence of respiratory failure is assumed.
Moderate:	An exacerbation treated with systemic corticosteroids with or without an antibiotic. If no blood gases are available the absence of respiratory failure is assumed.
Severe:	Type 1 respiratory failure with hypoxemia but no carbon dioxide retention or acidosis; PaO ₂ <60 mmHg and PaCO ₂ <45 mmHg
Very severe:	Type 2 respiratory failure, compensated, with hypoxia, carbon dioxide retention but no acidosis; PaO ₂ <60 mmHg, PaCO ₂ >45 mmHg and hydrogen ion concentration pH>7.35.
Life-threatening:	Type 2 respiratory failure, decompensated, with acidosis and carbon dioxide retention; PaCO ₂ >45 mmHg and hydrogen ion concentration pH<7.35.

Prior to starting antibiotics two to three ml of sputum was collected. As per the standard protocol Gram's stain, culture and sensitivity were performed on the sputum. Patients were followed up in the hospital over the time until they were discharged or till their death in the hospital. Mean length of hospital stay and in-hospital mortality were compared among the four groups. 30 day hospital readmission was also noted. Statistical data analysis was done using the latest

version of SPSS (Statistical Package for Social Science). Data was compiled using MS excel and analysed using IBM SPSS software version 20. Categorical data was expressed as frequency and percentage whereas continuous data was expressed as mean and standard deviation. Chi square test was applied to assess the difference between proportions. P value less than 0.05 were considered statistically significant.

Results

From December 2018 to May 2020 hundred patients of AECOPD were evaluated.

Table 2: Baseline characteristics of patients

Age (years)	Frequency (n=100)	Percentage
40-50	14	14.0
51-60	35	35.0
61-70	42	42.0
>70	9	9.0
Gender		
Male	85	85.0
Female	15	15.0
Place of residence		
Rural	35	35.0
Urban	65	65.0
Literacy		
Illiterate	34	34.0
Literate	66	66.0
Smoker		
Yes	81	81.0
No	19	19.0

Table 2 shows baseline characteristics of patients. Mean age of patients with AECOPD was 60.52±7.95 years. Male:female ratio was 5.66:1. Majority of the patients were smokers (81%).

Table 3: Association of severity of AECOPD with mean Blood Glucose level

Mean blood glucose level (mg/dl)	Severity of AECOPD				
	Mild	Moderate	Severe	Very severe	Life threatening
<110 (n=20)	11 (55)	9 (45)	0 (0)	0 (0)	0 (0)
110-125 (n=26)	10 (38.5)	13 (40)	3 (11.5)	0 (0)	0 (0)
126-160 (n=46)	1 (2.2)	18 (39.1)	15 (32.6)	9 (19.6)	3 (6.5)
>160 (n=8)	0 (0)	0 (0)	6 (75)	1 (12.5)	1 (12.5)
$\chi^2=56.51; p=0.001$					

Table 4: Correlations

R	R Square	Adjusted R Square	Std. Error of the Estimate	F	Sig.
0.634	0.402	0.396	0.821	65.84	0.001

Table 4 shows that mean blood glucose level had a positive correlation with increasing severity of AECOPD i.e. as the mean blood glucose level increased, severity of COPD exacerbation increased significantly (r²=0.402; p=0.001).

Table 5: Relative risk of exacerbation

Mean Blood glucose level (mg/dl)	Severity of AECOPD		
	Mild	Moderate	Severe + very severe + Life threatening
<126 (n=46)	21	22	3
>126 (n=54)	1	18	35
Relative risk for <126		1	0.14
Relative risk for >126		18	35
P value	0.001		

Table 5 shows Relative risk of moderate exacerbation increased 18 times and that of severe to life threatening exacerbation, 35 times when the mean blood sugar increased from <126 mg/dl to > 126 mg/dl. This difference was statistically highly significant ($p<0.001$).

Table 6: Association of LOHS with Mean Blood Glucose levels in patients with AECOPD

Mean Blood glucose level (mg/dl)	Length of Hospital stay (days)	
	<9 days*	>9 days*
<110 (n=20)	18 (90)	2 (10)
110-125 (n=26)	17 (65.4)	9 (34.6)
126-160 (n=46)	15 (32.6)	31 (67.4)
>160 (n=8)	1 (12.5)	7 (87.5)

$\chi^2=25.297$; $p=0.001$

Table 6 shows association between increased LOHS and Mean blood glucose levels. Significantly more number of patients with mean blood glucose level >126 mg/dl had LOHS > 9 days ($p<0.001$). *The median length of stay was 9 days.

Table 7: Association of 30 day hospital re-admission with Mean Blood Glucose levels in patients with AECOPD

Mean Blood glucose level (mg/dl)	30 day readmission	
	Yes	No
<110 (n=20)	0 (0)	20 (100)
110-125 (n=26)	0 (0)	26 (100)
126-160 (n=46)	4 (8.7)	42 (91.3)
>160 (n=8)	1 (12.5)	7 (87.5)

$\chi^2=4.69$; $p=0.196$

Table 7 shows that five patients were readmitted within 30 days of discharge from the hospital. However, no statistically significant association was found between mean blood glucose level and 30 day readmission rate ($p>0.05$). No mortality was reported in the study.

Table 8: Association between sputum culture and Mean Blood Glucose levels in patients with AECOPD

Mean Blood glucose level (mg/dl)	Sputum culture					
	Staph aureus	Pseudomonas	Klebsiella	Acinetobacter	MRSA	Sterile
<110 (n=20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	20 (100)
110-125 (n=26)	0 (0)	0 (0)	0 (0)	1 (3.8)	0 (0)	25 (96.2)
126-160 (n=46)	5 (10.9)	6 (13)	7 (15.2)	3 (6.5)	0 (0)	25 (54.3)
>160 (n=8)	4 (50)	2 (25)	0 (0)	0 (0)	1 (12.5)	1 (12.5)

$\chi^2=59.2$; $p=0.001$

Table 8 shows that below mean blood sugar of 126 mg/dl, sputum culture was sterile. Between 126 and 160 nearly half of the sputum samples were sterile. Above 160 mg/dl just 12.5% were sterile. Patients with mean blood glucose levels >126 mg/dl had more Gram Negative bacilli in the sputum sample ($p<0.001$). Staphylococcus aureus was cultured in 50% of the patients with blood glucose level >160 mg/dl. As the Mean Blood Glucose level increased, bacterial isolation became more frequent.

Discussion

We did this study to observe the correlation of blood glucose level with outcome of patients with Acute Exacerbation of COPD. Hundred patients of AECOPD were evaluated. Mean blood glucose level in patients presenting with AECOPD was 127.58 ± 18.89 mg/dl. With increasing mean blood glucose, the severity of Acute Exacerbation increased ($r^2=0.402$; $p=0.001$). Almost all patients with mean blood glucose greater than 160 mg/dl had severe (75%) to life threatening exacerbations (12.5%). The relative risk of moderate exacerbation increased 18 times and that of severe to life threatening exacerbation, 35 times when the mean blood sugar increased to > 126 mg/dl. Hajer Benabdel Ghaffar, et al. also found that patients with higher blood glucose concentration had more severe exacerbation and adverse clinical outcome [7]. Almost equal number of patients had less than 9 days LOHS (51%) or more than 9 days LOHS (49%). Patients with mean blood glucose level >126 mg/dl had significantly longer LOHS (greater than 9 days) when compared to patients with blood glucose <126 mg/dl. Baker EH et al also found that higher

blood glucose was significantly associated with prolonged duration of hospital stay and higher mortality rates [8]. Burt MG et al documented that for each 18 mg/dl increase in serum glucose levels, LOHS increased by 10% ($p<0.01$) [9]. Similarly, Parappil A et al also observed increased LOS in COPD patients with coexistent hyperglycaemia (7.8 days) [10]. There was no difference in 30 days readmission rates and mortality across the blood glucose spectrum. Kasirye Y et al [11] and Ahmed S et al [12] also did not find significant association between higher blood glucose levels and readmission rates in AECOPD patients. At low mean blood glucose level the sputum culture was mostly sterile for bacteria. At blood glucose level >126 mg/dl, more than half of the sample grew either single or multiple bacteria. At higher blood glucose level Gram negative bacteria were isolated two times more frequently than gram positive bacteria. At blood glucose level > 160 mg/dl Staphylococcus aureus (50%) was the predominant organism. S. Laukides, et al. in their study had shown that hospitalized patients with elevated blood glucose had more frequent isolation of gram negative bacteria. The greater susceptibility to GNB infections was due to frequent hospitalization and antibiotic use in their study group [13,14]. Baker EH et al found that participants in higher blood glucose groups were more likely to have more than one type of organism or Staphylococcus aureus isolated from sputum [8]. Similarly, Philips BJ et al also observed significant association between hyperglycemia and sputum colonization with MRSA and prolonged ICU stays (RR 2.1; 95% CI 1.2 to 3.8) [15].

Hyperglycaemia by predisposing to infection through systemic or local effects on host immunity or bacterial growth causes increased severity of AECOPD. This could be due to immune defects in people with high blood sugar. Decreased neutrophil and macrophage chemotaxis, phagocytosis, and killing and impairment in complement and cytokine responses to infection have been seen at higher blood glucose level [16]. Patients with AECOPD are prescribed systemic corticosteroid. Frequent exacerbators receive multiple courses of systemic corticosteroid, which is significantly associated with hyperglycaemia and other major adverse effects like increased risk of infections [17]. Infection may further lead to hyperglycaemia by causing peripheral insulin resistance and hepatic gluconeogenesis [18]. Although infections are said to be a major cause of exacerbations in COPD patients, absence of bacterial growth was seen in a very high percentage of patients in our study (71%). Still majority of the hospitalized patients received antibiotics and steroids. With lower mean blood glucose, sputum was mostly sterile. It is possible that many of the admitted patients with AECOPD may not require antibiotic. Furthermore, sterile samples could indicate allergic or viral exacerbations. Isolation of virus was not done in our study. Previous studies utilized either a single admission blood glucose or a single blood glucose obtained (fasting or nonfasting) during hospitalization. As blood glucose level in AECOPD patients on systemic corticosteroids peaks around afternoon and evening hours, our study utilized blood glucose measurement three times a day viz morning, afternoon and night over a five day period. Blood glucose measurements taken throughout the day more accurately capture a patient's glycemic status. Since we excluded diabetics, our study showed that even short term systemic corticosteroid use in AECOPD had adverse outcomes.

Conclusion

Our study concluded that higher mean blood glucose level was associated with increased severity of COPD exacerbation, longer LOHS and higher bacterial infection rates. No association was found between increasing mean blood glucose and 30 day readmission rate.

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