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Original article

Correlation of blood glucose levels on the outcome of patients with acute exacerbation of chronic obstructive pulmonary disease

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Abstract:

Background and objectives: Chronic obstructive pulmonary disease (COPD) is a common and preventable disease with increasing public health importance around the world. Many studies in the past have shown that hyperglycaemia is associated with poor outcomes from a wide range of acute illnesses. The present study was undertaken to determine the relationship between blood glucose levels and clinical outcomes in patients admitted with Acute Exacerbation of COPD (AECOPD).

Materials & Methods: The present hospital based prospective case series study was conducted on the patients admitted with the diagnosis of AECOPD under the Department of General Medicine in HSK Hospital& research centre, during the period of January 2014 to December 2014. Random blood sugar level by GOD-POD method (glucose oxidase - peroxidase, kits by Erba) method immediately at the time of admission, and other baseline investigations necessary to rule out other co-morbid conditions such as chest X-ray, ECG, 2D Echo, HbA1C, renal function test, complete blood count, sputum examination, spirometry and ABG.

Results: By comparing the mean length of hospital stay between the quartiles by using post hoc test there is no statistical significant relation found between the quartiles of RBS ≤140 mg/dl and 141-170mg/dl. (p=0.85). But there is statisticallyhighly significant relation between the quartiles of RBS ≤140 mg/dl with 171-200 mg/dl& ≥201 mg/dl with p value 0.01. Again, there is no statistical significance between other groups.

Conclusion: The conclusions arrived at from our study are that higher the admission RBS, longer was the median duration of stay in the hospital for patients with AECOPD. Admission RBS more than 170 mg/dl is detrimental in AECOPD patients. The mortality rate was also high in patients with AECOPD and higher admission RBS levels (more than 200 mg%).

Key words : AECOPD, Acute exacerbation of chronic obstructive pulmonary disease

Introduction

COPD is a major cause of chronic morbidity and mortality throughout the world. It has an extensive, adverse effect on both patients and the healthcare system with high resource utilization, which includes frequent clinician office visits, frequent hospitalizations due to acute exacerbations, and chronic therapy. Hence it has become a disease of increasing public health importance around the world.[1]With respect to patients, COPD causes physical impairment, debility, reduced quality of life, and death. It is the leading cause of death in the United States, killing more than 100,000 individuals and affects more than 16 million persons each year. Worldwide, COPD was the sixth leading cause of death in 1990. In previous studies it was projected to be the fourth leading cause of death worldwide by 2030.[2] However, it is currently third leading cause of death and affects > 10 million people in US. Estimates suggest that COPD will rise from the sixth to the third most common cause of death

worldwide by as early as 2020.[3]

Hyperglycemia associated with critical illness (also called stress hyperglycemia or stress diabetes) is a consequence of many factors, including increased cortisol, catecholamines, glucagon, growth hormone, gluconeogenesis, and glycogenolysis.[4] Insulin resistance may also be a contributing factor, since it has been demonstrated in more than 80 percent of critically ill patients.[5]Acute hypergly-caemia can occur in any acutely unwell patient, irrespective of baseline glucose tolerance, if the illness is sufficiently severe. Acute hyperglycaemia is associated with poor outcomes from a wide range of a-cute illnesses including myocardial infarction[6], stroke[7], trauma[8] and pneumonia.[9]Hyperglycaemia is th-us associated with a poor outcome from a widerange of acute illnesses. However, the relationship bet-ween blood glucose levels and clinical outcomes in AECOPD has not been fully established. Determ-ination of blood sugar is a simple procedure, requires no expertise, is inexpensive and importantly, It is a correctable factor, having a bearing on morbidity and mortality. Hence the present study was und-ertaken to determine the relationship between blood glucose concentrations and clinical outcomes in patients admitted with AECOPD.

Aims & objectives:

1. To compare the mean length of hospital stay in COPD patients with acute exacerbation, divided into groups according to severity of hyperglycemia.
2. To compare the mortality in these groups

Materials & Methods:

The present hospital based prospective case series study was conducted on the patients admitted with the diagnosis of AECOPD under the Department of General Medicine in HSK Hospital& research centre, during the period of January 2014 to December 2014.

Sample size is calculated using open epi software.

At 95% of confidence interval and 80% of power of the study.

According to Baker EH et al, the proportion of hyperglycemic patients with adverse outcome was 56%, P=56%. Absolute precision of 10%.

Sample size was calculated by using formula:

$n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$

The sample size calculated is 95, approximated to 100.

Selection criteria:

All the patients admitted with AECOPD irrespective of their admission glycemic status. COPD was designated by premorbid pulmonary function testing/ old documents if available. In the absence of documented air flow obstruction we used clinical criteria, clinical history with compatible physical findings and/or evidence of hyperinflation on chest radiograph in support of the diagnosis of COPD. Once the patient was stabilized the patients were subjected for spirometric studies and his/her COPD status confirmed. In patients with COPD, acute exacerbation was diagnosed by the following criteria.

- Recent rapid worsening of dyspnoea
- Increase in Sputum Purulence
- Increase in Sputum volume.

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Exclusion Criteria

- Patients with Pneumonia, Bronchial Asthma, Interstitial Lung Disease, Pulmonary tuberculosis andBronchiectasis.
- Patients of AECOPD with myocardial infarction and or reduced ejection fraction/CVA/requiring surgery/ Chronic Kidney Disease.

Methodology

Random blood sugar level by GOD-POD method (glucose oxidase - peroxidase, kits by Erba) method immediately at the time of admission, and other baseline investigations necessary to rule out other co-morbid conditions such as chest X-ray, ECG, 2D Echo, HbA1C, renal function test, complete blood count, sputum examination, spirometry and ABG.

- The length of hospital stay (in days) of each patient was recorded.
- If a patient expired, then it was recorded, with the date of mortality.

During hospital stay, the patients were treated by the consultant doctor as per requirement of the cases.The patients were followed up in the hospital over time until they were discharged or till death ensued. A composite adverse outcome was defined as, death or length of stay longer than the median length of stay for analysis.The data were entered in structured tables for comparison where the population in study was divided into groups or quartiles according to different age groups and blood glucose levels.

These quartiles are:

1) Random blood glucose ≤140 mg/dl (excluding hypoglycemia assumed as <60mg/dl),

2) Random blood glucose 141-170mg/dl,

3) Random blood glucose 171-200 mg/dl, and

4) Random blood glucose ≥200 mg/dl.

Patients were discharged when they are clinically stable and then the mean length of hospital stay was calculated for those patients corresponding to each quartile of random blood glucose. These values were then expressed in the tables with the standard deviations. Difference between the mean lengths of hospital stay was analyzed using a post hoc test.Comparison of the number of deaths also was done in a similar fashion, between the hyperglycemic and normoglycemic population. The hyperglycemia was assumed in this study as random blood glucose ≥140 mg/dl.Data were entered using Microsoft Excel version 2007 and SPSS 21 (statistical package for social studies) software and Statistical analysis was done using tables, graphs and diagrams. The study results were interpreted with the p-value. A p-value of <0.05 was considered statistically significant.

Results:

The present study included 100 patients admitted with the diagnosis of AECOPD during the study period i.e, from January 2014 to December 2014. The observations made were recorded and findings were tabulated as follows.

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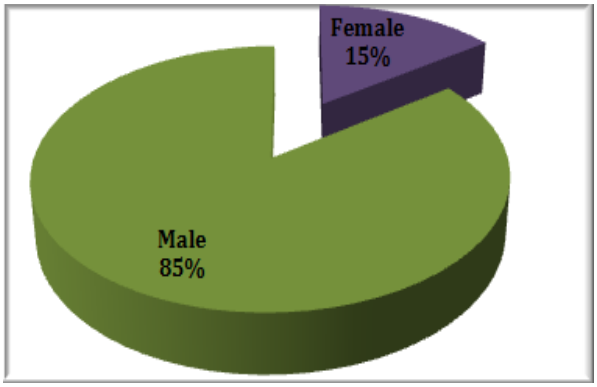
Table 1: Gender wise distribution

Sex	Frequency	Percent
Female	15	15.0
Male	85	85.0
Total	100	100.0

Figure 1: shows gender wise distribution

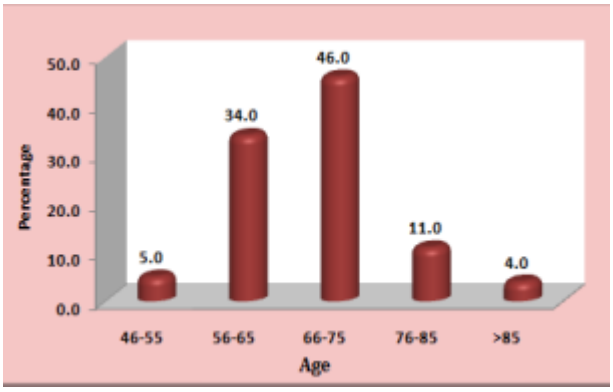


In the present study Majority of the study subjects were males (85%).

Table2: Age wise distribution of patients

Age	Frequency	Percent
46-55	5	5.0
56-65	34	34.0
66-75	46	46.0
76-85	11	11.0
>85	4	4.0
Total	100	100.0

Fig 2: shows age wise distribution of patients

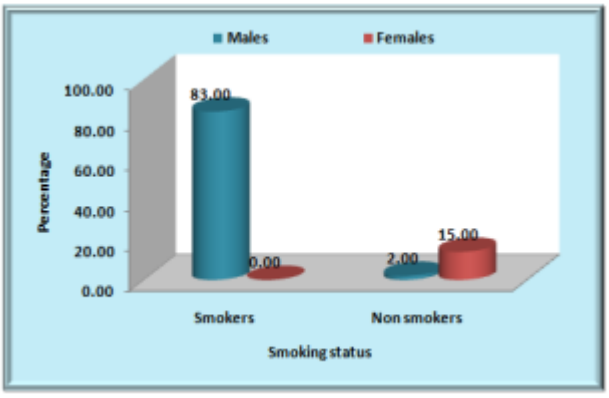


In the present study, majority of the study subjects belonged to the age group 66-75 years (46%) followed by 56-65 years which constituted 34%.

Table 3: Smoking among study population

Signs	Males		Females	
	No of persons	Percentage	No of persons	Percentage
Smokers	83	83.00	0	0.00
Non smokers	2	2.00	15	15.00

Fig3: shows smoking among study population



In the present study, out of the total 100 patients, 97.65% of male patients (n=83) were smokers, and 2.3% (n=2) were non smokers. None of the female patients smoked but had significant history of exposure to cooking fuels in their past. In all the smoking population, the number of pack years was more than 20.

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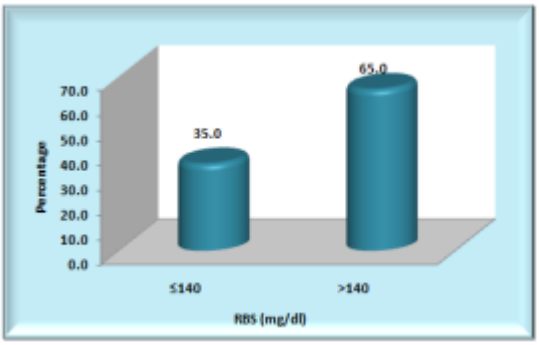
Table 4: Hyperglycemia among study population

RBS(mg/dl)	Frequency	Percent
≤140	35	35.0
>140	65	65.0
Total	100	100.0

Fig 4: hyperglycemia among study population.



In the present study, the hyperglycemia was assumed as random blood glucose levels >140 mg/dl. Out of 100 patients 35% (n=35) were normoglycemic and 65% (n=65) were hyperglycemic.

Table 5: Association between Sex & Age in hyperglycemia

Age	Sex		Total
	Female	Male	
46-55	0	4	4
	0.0%	100.0%	100.0%
56-65	3	18	21
	14.3%	85.7%	100.0%
66-75	4	22	26
	15.4%	84.6%	100.0%
76-85	1	9	10
	10.0%	90.0%	100.0%
>85	1	3	4
	25.0%	75.0%	100.0%
Total	9	56	65
	13.8%	86.2%	100.0%
Chi-square= 1.24 P-value=0.87 Inference=NS			

Fig 5: showing comparison of mean length of hospital stay among quartiles by using Anova

In the present study 4 (all males-100%) patients of age group between 46-55, 3(14.3%) female and 18(85.7%) male patients of age group 56-65, 4(15.4%) female and 22(84.6%) male patients of age group 66-75, 1(10%)female and 9(90%) male patients of age group 76-85 and 1 (25%) female and 3(75%) male patients of age group >85 years were found to be hyperglycemic i.e., RBS>140 mg/dl. However, There is no significant relation between age and sex in hyperglycemia (p= 0.87)

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Table 6: Comparison of mean length of hospital stay among Quartiles by using ANOVA

RBS Quartiles	Mean	SD	F	P-value	Inference
≤140	6.03	2.15	6.770	0.000	Highly Significance
141-170	6.59	1.91			
171-200	8.18	2.65			
≥201	8.46	2.58			

In the present study as the RBS levels increases the mean length of stay increased. Overall the mean length of hospital stay among different quartiles is found significant with p<0.001.

Table: 7 Comparison of mean length of hospital stay between the quartiles by using Tukey'spost hoc test

RBS Quartiles		P-value	Inference
≤140	141-170	0.85	NS
	171-200	0.01	HS
	≥201	0.01	HS
141-170	171-200	0.20	NS
	≥201	0.05	NS
171-200	≥201	0.98	NS

By comparing the mean length of hospital stay between the quartiles by using post hoc test there is no statistical significant relation found between the quartiles of RBS ≤140 mg/dl and 141-170mg/dl. (p=0.85). But there is statisticallyhighly significant relation between the quartiles of RBS ≤140 mg/dl with 171-200 mg/dl& ≥201 mg/dl with p value 0.01. Again, there is no statistical significance between other groups.

Table 8: Comparison of mortality according to Quartile levels

Age	RBS Quartiles (mg/dl)			
	≤140	141-170	171-200	≥201
46-55	0	0	0	0
	0.0%	0.0%	0.0%	0.0%
56-65	0	0	0	0
	0.0%	0.0%	0.0%	0.0%
66-75	0	0	0	1
	0.0%	0.0%	0.0%	3.2%
76-85	1	0	0	3
	2.9%	0.0%	0.0%	9.7%
>85	0	0	0	0
	0.0%	0.0%	0.0%	0.0%
Total	35	17	17	31

In the present study, out of 100 patients, 5 patients (5%) were expired. These 5 patients belonged to GOLD stage 4 as indicated by their past medical records. Among 5 patients, 4 patient's RBS at admission was more than 201 mg/dl, and one patients was <140 mg/dl. The percentage of mortality increased as the random blood glucose

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level increased. The highest percentage was in the population under RBS quartile of ≥201mg/dl. For the purpose of statistical analysis these five patients were not considered in calculating the mean length of stay.

Table 9: showing mortality among normoglycemic and hyperglycemic patients

Age	RBS (mg/dl)	
	≤140	>140
46-55	0	0
	0.00	0.00
56-65	0	0
	0.00	0.00
66-75	0	1
	0.00	20
76-85	1	3
	20	60
>85	0	0
	0.00	0.00

In our study, 80% deaths were in hyperglycemic population and 20% were in normoglycemic population. All the deaths were in more than 66 years of age group.

Discussion:

COPD is one of the leading causes of morbidity and mortality worldwide. Strategies to reduce mortality and length of hospital stay from AECOPD are being under trial. Previous studies have shown that in hospital mortality from AECOPD is predicted largely by fixed factors such as older age[10,11]male sex, co-morbidity, higher income[11] and arterial pH.[10] Hyperglycemia at the time of presentation is associated with a poor outcome in a wide range of acute illness. The relationship between blood glucose levels and clinical outcomes in AECOPD has not been fully established studies showed conflicting results. Hence the present study was undertaken to determine the relationship between blood glucose level at the time of admission and clinical outcomes in patients with AECOPD

A total of 100 patients were included in this study. 85% patients were males and the rest werefemales. Patients were between the age group of 46 to 90 years. The mean age of the population under study was 68.77 ± 8.19 years. This was similar to the observation made in a prospective study[12] carried out in 1997 at an acute care teaching referral center, in the province of Barcelona, Spain where the mean age of the population under study was 72.2 ± 9.25 years.Inour study, 83% were smokers and 17% non-smokers. The number of pack years in the smoking population was more than 20.This indicating the well-known fact that the incidence of COPD is more in smokers than in non smokers.

In the present study, the hyperglycemia was assumed as random blood glucose levels >140 mg/dl. Out of 100 patients 35% were normoglycemic and 65% were hyperglycemic. Among the hyperglycemics 22 patients(33.8%) were diabetics and 43 patients(66.2%) were non-diabetics indicating that the acute hyperglycaemia is frequently present in situations of stress, both in diabetic and in nondiabetic patients.[13]

In this study, we have divided all patients into four quartiles based on RBS at the time of admission, i.e., ≤140 mg/dl, 141-170mg/dl, 171-

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200 mg/dl, and ≥200 mg/dl and calculated mean length of hospital stay, which was compared among quartiles by using ANOVA, which showed statistical significance (p <0.05), indicating that there is a trend towards increased length of hospital stay as the admission RBS levels increases which is similar to the study[14] by Baker EH et al in which they have divided the patients in to quartiles i.e., <6 mmol/l (108mg/dl),6–6.9mmol/l(<126mg/dl), 7–8.9 mmol/l(126-162mg/dl) and >9 mmol/l(>162mg/dl) based on highest blood glucose levels measured either at admission or during the admission and also similar to the other studies by Parappil[15] and Burt.[16] The possible explanation for our observation is that, acute hyperglycemia is frequently present in situations of stress, both in diabetic and in nondiabetic patients.As far as the lungs are concerned, it is postulated that hyperglycemia affects the lungs by damaging capillaries and by the non-enzymatic glycosylation of collagen.[17] Hyperglycemia appears to cause cellular stress by various mechanisms, which could be detrimental to the lung.[18]These mechanisms will lead to impaired immunity and susceptibility to infections leading to adverse outcomes.But our study results are in contradictory to the studies by Kasirye[19]and Islam[20] where they observed that there is no relation between blood glucose levels and length of stay or adverse outcomes. 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 in different studies, management approaches and choice of medication.

By comparing the mean length of hospital stay in between quartiles by using post hoc test there was no statistical significance between the quartiles of RBS ≤140 mg/dl and 141-170mg/dl. (p=0.85). But there was statistically significant relation between the quartiles of RBS ≤140 mg/dl with 171-200 mg/dl& ≥201 mg/dl with p value 0.01. Again, there was no statistical significance between other groups. This implies that RBS more than 170 mg/dl is detrimental in AECOPD patients based on our study results. However, this is yet to be established with certainty. Baker in his study found that RBS>7 mmol/l(126 mg/dl) is detrimental in AECOPD patients.[14] A prospective study[21] by Gao L in China from may2007 to august 2013 found that intensive glucose control treatments are associated with adverse clinical outcomes in patients admitted with diagnosis of AECOPD. In this study, the subjects in the intensive glucose control group were treated using insulin as required such that the fasting blood glucose(FBG) was controlled to 4.4 – 6.1 mmol/l (80-110 mg/dl) and the post-prandial blood glucose was <8 mmol/l (144mg/dl). There was significant incidence of hypoglycemia and hypokalemia in intensive glucose control group. Which indirectly supports our result that the blood glucose level if maintained less than 170 mg/dl, than strict glycemic control (<140 mg/dl) may help for better outcome. Archer, in his prospective, non randomized, single arm studyof intensive glycemic control in AECOPD patients demonstrated that intensive glucose control can

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be achieved with in the acute medical ward with a similar safety and efficacy to that achieved with patients admitted to an intensive care unit, and the control of blood glucose could potentially have some benefit in AECOPD patients.[22]In our study, total deaths were 5, among 100 patients. The crude mortality rate of this study was 5%. All these 5 patients belonged to GOLD stage IV as indicated by their past medical records. Among 5 patients, 4 patient's RBS at admission was more than 201 mg/dl, and one patients was <140 mg/dl. The percentage of mortality increased as the random blood glucose level increased. The highest percentage was in the population under RBS quartile of ≥201mg/dl. All the deaths were in more than 66 years of age group.As this was a prospective study done within a limited period of time, the number of patients who were selected according to inclusion criteria was not adequate enough to produce statistically very significant results. This study was performed in a single hospital, in the population of North Karnataka which limits its generalizability to other population. Even though we were able to standardize the timing of blood glucose measurement (i.e., at the time of admission) this does not completely exclude the confounding effects of corticosteroids as we were not able to determine whether participants were taking steroids before admission and the severity of the disease was not compared because of the lack of recent spirometric reports in few patients.

Conclusion:

The conclusions arrived at from our study are that higher the admission RBS, longer was the median duration of stay in the hospital for patients with AECOPD. Admission RBS more than 170 mg/dl is detrimental in AECOPD patients. The mortality rate was also high in patients with AECOPD and higher admission RBS levels (more than 200 mg%).

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