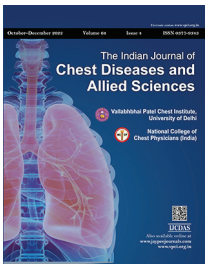
ORIGINAL ARTICLE



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Effect of Hyperglycemia on the Duration of Hospital Stay and Rate of Mortality in Patients of Chronic Obstructive Pulmonary Disease in Acute Exacerbation: A 1-year Hospital-based Observational Study

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is not only a respiratory disease but is also a systemic disease associated with comorbidities such as diabetes mellitus (DM), hypertension, osteoporosis, etc. Diabetes being one of the comorbidities, COPD is thought to be a causative factor for developing insulin resistance. Similarly, poor glycemic control is associated with worsened COPD outcomes. Thus, this study has been taken up to analyze the effect of hyperglycemia on the duration of hospital stay and rate of mortality, and other outcomes in patients with COPD with exacerbation.

Methods: It was an observational study conducted for 1 year in KLES Dr. Prabhakar Kore Hospital & Medical Research Centre, Belagavi, Karnataka, India. A total of 84 patients were enrolled and divided into two groups based on the mean random blood sugar (RBS) levels. Group I had 40 patients with mean RBS <250 mg/dL and group II had 44 patients with mean RBS ≥250 mg/dL. Outcomes and variables of the patients with COPD were compared between both groups.

Results: Patients in group II had poor outcomes compared to group I. The mean duration of hospital stays in groups I and group II were 5.43 and 7.34, respectively, with a significant $p < 0.0001$. The mean duration of intensive care unit (ICU) stay was 3.33 and 4.47 in groups I and II, respectively, which was statistically significant. The rate of mortality in groups I and II was 5.00 and 11.36%, respectively.

Conclusion: Patients with hyperglycemia had an increased duration of hospital stay and rate of mortality. Optimal glycemic control plays a significant role in patients with COPD in reducing the severity of exacerbation and mortality.

Keywords: Chronic obstructive pulmonary disease in acute exacerbation, Duration of hospital stay, Duration of intensive care unit stay hyperglycemia, Random blood sugar, Rate of mortality.

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Abbreviations used in this Article

COPD = Chronic obstructive pulmonary disease; DM = Diabetes mellitus; FBS = Fasting blood glucose; RBS = Random blood sugar (RBS); ICU = Intensive care unit; T2DM = Type 2 diabetes; MDI = Metered dose inhaler; NIV = Non-invasive ventilation; GOLD = Global Initiative for Obstructive Lung Disease; ADA = American Diabetes Association; PPBS = Post prandial blood glucose; WBC = White blood cell; IV = Intravenous.

Introduction

The COPD represents a significant public health challenge and is a major cause of hospital admissions all over the world. It is the third principal cause of mortality all over the world currently.[1] The load of this disease is estimated to raise in the coming decades because of continued exposure to risk factors and the aging of the population.[2] The crude prevalence of COPD in India increased by 29% from 1990 to 2016. The COPD and DM share relevant features in their genesis and course due to their inflammatory pathology. Patients with COPD are predisposed to develop impaired glucose tolerance due to several risk factors such as obesity, a sedentary lifestyle, smoking, oxidative stress, and corticosteroid therapy. The COPD has a 26–27% higher risk of death when it coexists with type 2 diabetes (T2DM). Treatment of exacerbation of COPD may worsen the course of DM, as systemic steroids, which are frequently administered to COPD cases after their admission owing to acute exacerbation, elevate the risk of hyperglycemia.[3]

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Both COPD and DM pose a huge challenge to physicians owing to their growing incidence in India and Western countries. Many studies done in countries outside India have signified the poor outcome of patients with COPD with coexisting DM compared to those without DM. So, this study has been taken up to assess the effect of hyperglycemia on the outcomes of acute exacerbation of patients with COPD in the Indian population.

Objectives

The primary objective was to assess the effect of hyperglycemia on the duration of hospital stay and the rate of mortality in patients with acute exacerbation of COPD. Other objectives include duration of non-invasive ventilation (NIV) and steroid requirement, duration of ICU stay, and other significant outcomes.

Methodology

A 1-year observational study was conducted in KLES Dr. Prabhakar Kore Hospital & Medical Research Centre, Belagavi, Karnataka, India. It was a longitudinal observational study conducted between January 2019 and December 2019. The sample size of the study was 84. The data were gathered from all the patients of COPD who were in acute exacerbation with previously or newly diagnosed DM and admitted to the hospital. All the patients with COPD who were admitted for acute exacerbation and previously or newly diagnosed DM have been included in the study.

Exclusion Criteria

- Patients with older or active pulmonary tuberculosis infection.
- Patients with chronic lung disorders other than COPD.
- Patients with HIV and other immunosuppressive disorders.
- Patients with hypertension and other comorbidities other than DM.
- Patients with diabetic nephropathy and retinopathy and all other complications of DM.

The COPD was confirmed based on the Global Initiative for Obstructive Lung Disease (GOLD) 2018 criteria which state the presence of post-bronchodilator FEV1/FVC value below 0.70 and the spirometry value included was done prior to the study and not during exacerbation. All patients with previously or newly diagnosed diabetes mellitus were included in the study. The diagnosis was based on the American Diabetes Association (ADA) criteria for diagnosing DM (Table 1). The ADA criteria for the diagnosis of DM are as follows:

- Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL) or
- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or
- HbA1c ≥6.5%

The patients were classified into two groups based on the mean random blood glucose levels of the entire hospital stay period (Table 2). The RBS levels were checked thrice daily during the admission period and the mean value was calculated from all the sugar levels. Patients with mean RBS <250 mg/dL were included in group I. Patients with mean RBS ≥250 were included in group II.

Duration of hospital stay, rate of mortality, and all other outcomes were compared and evaluated among the two groups. All patients involved in the study were classified further into two groups, namely, controlled and poorly controlled diabetic patients. Those with HbA1c below 7.5 were included in the controlled diabetic patients' group and those with HbA1c ≥7.5 were included in the poorly controlled diabetic patients' group (Table 3). They were compared and analyzed with the outcomes during the hospital stay. The ethical clearance was obtained from the Ethical and Research Committee, KLES Dr. Prabhakar Kore Hospital & Medical Research Centre, Belagavi, Karnataka, India before the initiation of the study. The procedures followed are in accordance with the ethical standards laid down by the committee.

Statistical Analysis

For the continuous quantitative variables – mean and standard deviation – were calculated. For the use of comparison, if the data are classified into two groups with respect to certain qualitative characteristics, the continuous variables will be compared using suitable tools of statistics. Suitable graphs were used to depict the comparison. The categorical data will be expressed in terms of rates, ratios, and percentages. The association between the outcome, clinical, and demographic characteristics were tested using the test of proportion or Fisher's exact test. For all the tests the *p*-values that are less than 5% (0.05) were considered significant.

Results

A total of 97 patients with COPD coexisting with DM were included in the study. A total of 11 patients were excluded due to other lung and cardiovascular diseases. Three patients took the decision against medical advice discharge during the study. So, 13 patients were excluded and 84 patients were considered in the final analysis. The mean age in group I was 68.47 ± 8.20 years and in group II was 67.57 ± 11.74 years. The mean age of all the study patients was 68.00 ± 10.16 years. In group I, the number of male patients was 28 (70%) and in group II, there were 29 (65.91%) patients. The mean BMI of the overall patients was 24.71.

Primary Outcomes

The mean duration of stay in the hospital was higher in group II when compared to group I. The mean duration in group A was 5.43 days and in group II was 7.34 days which was highly statistically significant with $p = 0.0004$. The total mean duration of all the patients in the study was 6.43 days. The rate of mortality in group I was 5.00% and in group II was 11.36%. The total number of patients who expired was 7. The overall mortality of the study patients was 8.33%. The *p*-value was not statistically significant.

Secondary Outcomes

The mean duration of ICU stays in groups I and II was 3.33 and 4.47, respectively. Group II patients had a longer duration of ICU stay compared to group I with a $p = 0.0757$ which was not statistically significant. The total mean duration of stay in the ICU was 4.04 days.

The mean duration of treatment with NIV in groups I and II was 2.29 ± 0.76 and 3.14 ± 1.29, respectively, with a $p = 0.1240$ which was not statistically significant. The number of patients who were treated with NIV in group I was 7 and in group II, it was 14 which was double the number of patients in group I. The number of patients who required intubation for acute exacerbation of COPD in groups I and II was 4 10.00 and 8 (18.18%), respectively, with a $p = 0.2845$.

The number of participants who received above 1 antibiotic during the hospital stay in groups I and II was 17 (42.50%) and 22 (50%), respectively; $p = 0.5728$ which was not statistically significant. The mean duration of intravenous (IV) steroids given during the hospital stay was 4.33 ± 1.14 days in group I and 5.77 ±

Table 1: Comparison of baseline characteristics of both groups

Characteristics	*Group I*	*Group II*	*Total*	*p-value*
Number of patients	40	44	84	
Age (mean ± SD)	68.475 ± 8.20	67.57 ± 11.74	68.00 ± 10.16	0.5676
Number of males	28 (70%)	29 (65.91%)	57 (67.86)	
Number of females	12 (30%)	15 (34.09%)	27 (32.14)	
BMI (mean ± SD)	23.9 ± 3.88	25.45 ± 3.14	24.71 ± 3.58	0.0461
Smokers among males	21 (77.78%)	25 (83.33%)	46 (80.70)	0.2342
FEV1% (mean ± SD)	52.87% ± 11.43%	51.44% ± 8.81%	52.25 ± 10.28%	0.6091
FEV1/FVC (mean ± SD)	0.60 ± 0.05	0.62 ± 0.05	0.61 ± 0.05	0.1438
COPD duration (years)	5.57 ± 4.44	4.77 ± 3.86	5.15 ± 4.14	0.3828
Number of patients using MDI	8 (20%)	11 (25%)	19 (22.62)	
HbA1c (mean ± SD)	7.2 ± 0.75	8.49 ± 1.52	7.87 ± 1.37	<0.0001
Number of patients using insulin	18 (45%)	28 (63.64%)	46 (54.76%)	
Diabetes duration	4.28 ± 2.59	6.57 ± 4.52	5.64 ± 4.00	0.0258
Mean FBS	195.68 ± 26.15	183.38 ± 23.45	205.68 ± 24.06	<0.0001
Mean PPBS	310.06 ± 26.15	283.98 ± 34.09	334.82 ± 39.28	<0.0001

FBS, fasting blood glucose; MDI, metered dose inhaler; PPBS, post prandial blood glucose

Table 2: Comparison of outcomes of the study among the two groups based on mean random blood sugar levels

Characteristics	*Group I (Mean RBS <250 mg/dL)*	*Group II (mean RBS > 250 mg/dL)*	*Total*	*p-value*
Duration of hospital stay (mean ± SD) (Number of days)	5.43 ± 1.71	7.34 ± 2.82	6.43 ± 2.53	0.0004
Duration of ICU stay (mean ± SD) (Number of days)	3.33 ± 1.12	4.47 ± 1.60	4.04 ± 1.52	0.0475
Duration of NIV (mean ± SD) (number of days)	2.29 ± 0.76	3.14 ± 1.29	2.86 ± 1.20	0.1240
Rate of mortality % (number of patients)	5.00 (2)	11.36 (5)	8.33 (7)	0.2919
Number of patients treated with >1 antibiotic (%)	17 (42.50)	22 (50.00)	39 (46.43)	0.5728
Duration of IV steroids (mean ± SD) (number of days)	4.33 ± 1.14	5.77 ± 1.49	5.08 ± 1.51	<0.0001
Total WBC counts (mean ± SD)	23.90 ± 3.88	25.45 ± 3.14	24.67 ± 6.62	0.0461
Oxygen saturation % (mean ± SD)	90.65 ± 6.82	87.98 ± 7.09	89.32 ± 6.96	0.0826
Number of patients who required invasive mechanical ventilation (%)	4 (10.00)	8 (18.18%)	12 (14.29)	0.2845

Table 3: Comparison of the outcomes based on HbA1c levels

Characteristics	*HbA1c < 7.5 (controlled diabetes)*	*HbA1c ≥ 7.5 (poorly controlled diabetes)*	*Total*	*p-value*
Duration of hospital stay (mean ± SD) (number of days)	5.59 ± 2.00	7.35 ± 2.06	6.43 ± 2.53	<0.0001
Number of exacerbations in the last 1 year (mean ± SD)	2.86 ± 1.29	3.13 ± 1.24	2.99 ± 1.32	0.0154

1.49 days in group II with a highly significant $p < 0.0001$. The mean SpO_2 during the hospital stay in group I was 90.65 ± 6.82% and in group II was 87.98 ± 7.09%, whereas the $p = 0.0826$ which was not statistically significant. The overall mean SpO_2 among the study groups was 89.31%. The mean white blood cell (WBC) total count in group I was 23.90 ± 3.88, whereas in group II, it was 25.45 ± 3.14; $p = 0.0461$ which was statistically significant.

In the sputum culture, the predominant microorganisms grown were *Streptococcus pneumoniae* and *Haemophilus influenza* with 4.76% each of them followed by *Acinetobacter baumanni,* and *Moraxella catarrhalis* with 2.38% each of the organisms. The majority of them in the study had a result of either no growth or commensals isolated in the culture**.**

Based on HbA1c levels, the study patients were divided into two groups and compared. Patients with HbA1c < 7.5 were taken as the controlled group and those with HbA1c ≥ 7.5 were included in the poorly controlled group. The total mean duration of stay in the hospital in controlled diabetic patients was 5.59 ± 2.00 and in

poorly controlled patients, it was 7.35 ± 2.06; $p < 0.0001$. The mean number of exacerbations in the controlled group was 2.86 ± 1.29 whereas in the poorly controlled group, it was 3.13 ± 1.24.

Discussion

Chronic obstructive pulmonary disease is thought to be a causative factor for developing insulin resistance leading to the onset of DM. Treatment for acute exacerbation of COPD may deteriorate the course of DM, as systemic glucocorticoid steroids, which are frequently administered to COPD cases after their admission owing to acute exacerbation, increase the risk of hyperglycemia.

On the other hand, poor glycemic control is considered as an independent factor that impairs pulmonary structure and function affecting it negatively. Diabetes is associated with an increased risk of pulmonary infections, disease exacerbations, and worsened COPD outcomes. So, this study has been taken up to analyze the effect of glycemic control on the outcomes of hospitalized patients with COPD admitted with exacerbation.

The majority of the patients in our study belonged to the 60–69 age group with 45.24% of them in it, whereas it was 13.10% in the 50–59 years age group. As age increases, the severity of exacerbation and blood sugar levels increases which may be due to the increased insulin resistance as age increases. Male-to-female ratio was almost 2:1 indicating the male predominance in our study.

The overall mean HbA1c value in our study was 7.87 which falls in the category of poorly controlled diabetics. More studies had authenticated that glycemic control among patients with COPD patients was poor and especially the patients in India.

The mean exacerbation in the last 1 year in the controlled diabetes group was only 2.86 ± 1.29 whereas in the poorly controlled group, it was higher with a mean value of 3.13 ± 1.24. The *p*-value in our study for mean exacerbation was 0.0154 which was statistically significant. In our study, most of the patients in class I (severe form) of Anthonisen's classification belonged to group II with poor glycemic control. To compare with the other studies, a study done by Küpeli et al.[4] observed 106 patients with COPD comprising 29 with metabolic syndrome and 77 with no comorbidities for a year and it resulted in the increased mean exacerbation frequency of 2.4 in those with metabolic syndrome and frequency of 0.68 in those without the syndrome.

In our study, the mean duration of stay in the hospital was higher 7.35 ± 2.06 in the poorly controlled diabetic patients. The mean duration of stay in the hospital in group II was 7.34 ± 2.82 whereas in group I it was on the lower side with a mean duration of 5.43 ± 1.71. The mean duration of hospital stay was statistically significant with $p < 0.0001$.

Umpierrez GE et al.[5] mentioned in their study that hyperglycemia is linked with a longer duration of stay in the hospital, elevated morbidity, and increased complications whereas, in the same study, optimal control of blood glucose levels of less than 150 mg/dL decreased the antibiotic requirement and in-hospital mortality.

Ferreira et al.[6] studied the influence of glycemic variation on the duration of stay in the hospital and the rate of mortality in stable patients of COPD or community-acquired pneumonia. The mean duration of stay in the hospital was 10 days with more than 41% of the patients having HbA1c above 8.0%.

Compared to above-mentioned studies, our study had a lesser mean duration of hospital stay among all the patients which might be due to the lower sample size, efficient management, and also due to some of the patients included in our study being with controlled diabetes.

The probable explanation can be due to an increased number of infections, severe exacerbations, and sepsis leading to multiorgan dysfunction and uncontrolled blood sugar levels in group II. This might have happened due to increased antibiotic and corticosteroid usage in those patients. Hyperglycemia further worsens infection in them by causing protein glycosylation, the deranged function of leukocytes through its impairment, and activation of pro-inflammatory genes through transcription factors.

We had observed an increased usage of steroids in our study and especially in group II. As severe exacerbations and lung damage were observed more among group II patients, their steroid doses were higher in them. This higher steroid dosage could have worsened the glycemic control and also aggravated the respiratory muscle weakness causing myopathy. The neuromuscular weakness secondary to steroid-induced myopathy should be considered as a principal factor for prolonged ICU stay in our study.

Another primary outcome was the rate of mortality which was 11.36% in group II whereas it was 5.00% in group I. Among the 84 patients in total, 7 of them died which shows an overall mortality rate of 8.33%.

Gudmundsson et al.[7] mentioned in a study that out of 416 patients with COPD, 122 patients had died during the follow-up, and the major cause of mortality was DM which was present in up to 16% of them. The rate of mortality was statistically significant with $p = 0.03$.

In one of the studies by Islam et al.[8] showed that the mean random blood glucose levels of inpatient hospital deaths among the acute exacerbation of patients with COPD were 192 ± 97 whereas among the survivors the mean value was 151 ± 69.6. Compared to the mentioned studies, ours was not statistically significant, but still, there was a relative increase in the rate of mortality in patients with poor glycemic control. It stresses the requirement of tight blood glucose control for all patients to reduce the hospital stay and in-hospital mortality.

In our study, we observed an increased duration of stay in the ICU among the patients in group II compared to group A. The mean duration of group II was 4.47 ± 1.60 days and the mean value of group I was 3.33 ± 1.12 days. The mean RBS in group II was 276.06 ± 12.08 and the mean value of group I was 225.00 ± 12.08. Poor glycemic control in group II correlates with the above data for increased duration of stay in the ICU.

The probable explanation may be due to the presence of increased severity of exacerbations, prolonged ICU stays infections with increased resistance to antibiotics, and sepsis associated with multiorgan dysfunction in the group II patients. The probable causative factor could have been the poorly controlled blood sugars promoting aggravated lung injury, inflammation leading to persistent hypoxemia, and worsening of the general condition.

Glycemic variation increases oxidative stress, damages relaxation of vasculature which is endothelial mediated and increases inflammatory cytokine release.[9] It is also easily evident that tight glycemic control in ICU could decrease the ICU stay and more importantly reduce the incidence of hospital-acquired pneumonia.

In our study, the major cause of exacerbation was found to be an infection which was up to 33.33%. Other causes include indoor and outdoor pollution present in 11.90 and 10.71%, respectively.

Among the patients with infection, *S. pneumoniae* was found in the sputum culture of 4 patients and *H. influenza* was cultured in 4 patients. These were the two predominant organisms cultured.

In our study, the mean NIV duration in group II was 3.14 ± 1.29, and the mean duration in group I was 2.29 ± 0.76. Although not statistically significant, the duration of the NIV requirement was higher among the group II patients. There exists a relative correlation between poor glycemic control and increased duration of NIV requirement.

Most of our patients admitted into ICU for either pneumonia or respiratory failure were presented with exacerbation in the emergency room with uncontrolled blood sugars. Tight glycemic control has a significant effect on the improvement of the patient's condition during sepsis and respiratory failure.

It is easily evident that the duration of stay in the hospital and rate of mortality will be higher in poorly controlled diabetic patients and our study proved the above statement with statistically significant values. The explanation for the poor outcomes which we found in our study could be due to longer duration of treatment with corticosteroids for the patients in exacerbation, increased insulin resistance causing persistent raise in blood glucose levels.

Limitations

- The study was performed in a tertiary care center. It might not represent the overall general population.
- Both controlled and poorly controlled diabetic patients classified based on HbA1c were included in groups I and II. This might have influenced the outcomes among the study patients.
- Group II had more patients in class I exacerbation which is more severe when compared to group I. This difference in severity might have influenced the results of the study.
- The confounding factors like secondary infection, and use of corticosteroids might have extended the hospital duration.

Conclusion

- The duration of hospital stay and rate of mortality were significantly increased in proportionate to the increased plasma glucose levels and in patients with poor glycemic control.
- Hyperglycemic patients with COPD had increased severity of exacerbation and risk of infection.
- Strict glycemic control and monitoring of blood sugars will help in reducing the exacerbations and hospital admissions among patients with COPD.

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