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PROSPECTIVE STUDY OF HYPERGLYCEMIA AND ITS IMPACT ON THE CAUSATION OF SEVERE EXACERBATIONS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PATIENTS ATTENDING A TERTIARY CARE HOSPITAL

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ABSTRACT
Background: Hyperglycemic states are always associated with sudden onset of illnesses of both infectious and non-infectious nature. Chronic obstructive pulmonary disease is a chronic, lifelong suffering illness with sudden exacerbations. **Objectives:** To compare the affiliation of hyperglycemia with the chance of sudden exacerbations in sufferers with an established diagnosis of obstructive airway disease (COPD). **Materials Methods:** A total of 263 patients with an established diagnosis of COPD were taken into this observational study. The duration of the study extended between Jan. 2022 to July 2023. Sufferers were divided into 3 classes following the guidelines of the American Diabetes Association; those classes were: low HbA1c level class (n=102), moderate HbA1c level (n=83), and severe HbA1c level (n=74). **Results:** Among the 263 participants, 72 (27.4%) suffered severe exacerbation. The share of sufferers tormented by a minimum of one episode of intense and sudden exacerbation becomes extensively higher among participants with high (36.3%) and moderate HbA1c levels (24.7%) when compared with low HbA1c levels (22.6%). On the MCRA, high HbA1c levels (HR=2.65, 95% CI: 1.92–4.31; P<0.01) and moderate HbA1c levels (HR=2.06, 95% CI: 1.64–3.29; P<0.01). Participants with hyperglycemia were significantly associated with a higher risk of the next severe exacerbation compared with a euglycemic state. **Conclusion:** irrespective of current/previously established diagnosis of diabetes, hyperglycemic states are associated with a higher risk of severe exacerbation in patients with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a health condition recognized by continuous, partially irreversible airflow obstruction and inflammation of the lung tissues and smaller bronchi [1]. It is now established to be the 3rd leading contributory factor for the cause of death worldwide, amounting to a total of over 30 lakh deaths in 2019, and a considerable number contributed from developing and third-world countries

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[2] in COPD patients cause of repeated hospital admissions. Untimely death is due to sudden and intense exacerbation of COPD, also called acute exacerbation (AECOPD) [3]. Moreover, intense exacerbation is connected to excessive hazard of premature death and an average survival of 3.6 years [4]. Thus, finding out and minimizing the hazardous elements for an excessive exacerbation is important to enhance the outcomes in those suffering from COPD. Severe exacerbations often can be caused by a variety of proven etiological causes, which comprise repetitive infections of upper and lower airways, exposure to allergens, previous severe exacerbations, poor compliance to medication, and co-morbidities [5] in COPD patients, most common and grave co-morbidity is Diabetes mellitus. The rates of detecting hyperglycemia among patients who were hospitalized with the diagnosis of AECOPD are in the range between 18% in Switzerland [6] to 40% in India, [7] these prevalence rates were comparatively much higher in hospitalized patients than what were observed in the general population [8]. Whatever existing data reported to date on COPD has reiterated that COPD patients with high levels of blood sugar are prone to develop severe exacerbations and mortality. In the hospitals [9], despite this, minimal studies were conducted to establish the existence of any correlation between hyperglycemia and the development of severe exacerbations in COPD among the Indian population. Hence, the present study aims to assess the impact of hyperglycemia with or without a previous diagnosis of diabetes and the causation of severe exacerbations in patients with COPD.

MATERIALS AND METHODS

This prospective, observational study was conducted on successive patients with established diagnoses of COPD who were admitted into the Department of Pulmonology, Narayana Medical College Hospital, with a diagnosis of severe exacerbation of COPD between Jan. 2022 and July 2023. The duration of the study is 18 months, as patients are required to meet the required number of patients to meet the power of the survey as per sample size calculation.

Inclusion criteria:

1. Patients of both sexes and more than 40 years old.
2. Patients with previous diagnosis of COPD.
3. Diagnosis of COPD exacerbation according to the criteria proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.
4. Patients willing to give valid informed consent.

Exclusion criteria

1. History of bronchial asthma / any other respiratory ailments.
2. Patients suffering from any systemic ailments requiring long-term steroid therapy.
3. Patients with FEV1/FVC value of< 0.7
4. Suffering from any malignancy.
5. Confirmatory pregnancy or within a month after delivery.
6. Patients are not willing to give valid consent.

The patient sample for the following study was recruited after satisfying the inclusion and exclusion criteria mentioned above.

DATA COLLECTION AND OUTCOMES

A total of 263 patients who were fulfilling the inclusion/ exclusion criteria were recruited into the study. The study population was divided into three groups per their estimated HbA1c level at admission. 102 patients with HbA1c <5.7, 83 patients with HbA1c values between 5.7–6.4%, and 78 people with HbA1c levels≥6.5% were classified based on the American Diabetes Association's Standards of Care of diabetes mellitus. Baseline patients' characteristics comprising of age, sex, body mass index, smoking habit, COPD severity based on GOLD staging, COPD assessment test (CAT) score [11], evidence of a total number of previous acute COPD exacerbations occurred in the past 12 months. History is suggestive of the existence of any other comorbidities recorded. All subjects were followed up consecutively for the next 12 months. The development of acute exacerbations during the follow-up period was assessed using telephone interviews or a review of the hospital records at the end of each month. Any patient requiring admission of a minimum of 24 hours duration in the clinical setup with a diagnosis of COPD exacerbation is the prerequisite to call it an acute exacerbation.

STATISTICAL ANALYSIS

Continuous variables are calculated by using mean ± SD. All categorical variables were summarized as percentages and compared by chi-square test. Multivariate Cox regression analysis was used to evaluate the value of HbA1c for the time of the next COPD severe exacerbation. The relationship between HbA1c level and the risk of severe exacerbations in different GOLD stages and diabetes status were further evaluated, and additional multivariate Cox regression analyses were performed. a P value of less than 0.05 was considered significant. All statistical analyses were performed by using the SPSS statistical

software program package (SPSS version 20.0 for Windows, Armonk, NY: IBM Corp.) [12]

Ethics Approval and Informed Consent

The study was formulated after obtaining approval from the institutional ethical committee. With reference details of a letter dated 10-2-2021 with letter no. NMC/ADM/ETHICS/approval/ 003/12/2021. Written informed consent was obtained from all participants satisfying inclusion criteria before they were recruited into the study. Patients and their relatives were told that unwillingness to participate in the study would not result in any deviation in treatment protocols. No invasive procedures were carried out. No additional benefits were provided to patients or their relatives as part of the study. Data safety norms were followed to preserve the confidentiality and privacy of the patient.

Table 1 Study participants Baseline details

	Total	HbA1c level			p-value
		Low	Moderate	High	
N	263	102	83	73	
Age, years	66.4±11.7	67.4±12.4	66.3±12.9	68.5±10.9	0.37
Gender, n (%)					
Male	208(78.9%)	80(78.4%)	65 (78.8%)	63 (79.6%)	0.96
Female	56 (21.1%)	22 (21.6%)	18 (21.2%)	16 (20.4%)	
BMI, kg/m^2	26.0±2.3	25.3±3.3	27.1±2.2	25.8±1.9	<0.01
Smoking status, n (%)					
Never-smoker	74 (29.8%)	29 (30.4%)	23 (29.7%)	22 (29.3%)	0.52
Ex-smoker	133 (50.6%)	49 (48.5%)	41 (48.5%)	43 (55.4%)	
Smoker	56(19.6%)	24(21.1%)	20(21.8%)	12(13.5%)	
Disease duration of COPD, n (%)					
<3 years	95 (35.2%)	21(22.10%)	32(34.6%)	42(43.3%)	0.07
3-5 years	109(40.4%)	44(43.6%)	36(44.0%)	29(36.9%)	
>5 years	59(24.4%)	11(33.0%)	21 (21.4%)	27(19.8%)	
Number of admissions in last one year					
<2	200 (77.0%)	50 (83.9%)	66(75.2%)	84 (69.4%)	0.02
>2	63 (23.0%)	15 (18.1%)	21 (24.8%)	23 (30.6%)	
GOLD stage, n (%)					
Stage 1	13 (4.8%)	2(3.4%)	4(7.1%)	7(8.1%)	0.97
Stage 2	72 (27.2%)	20 (29.8%)	24 (25.1%)	28 (25.1%)	
Stage 3	122 (46.4%)	36 (43.6%)	40 (46.3%)	46(46.8%	
Stage 4	56 (21.7%)	12(23.2%)	20 (21.6%)	24 (21.0%)	
CAT score, n (%)					
0-10	25 (10.5%)	6 (10.6%)	9 (10.1%)	10 (10.2%)	0.75
11-20	117 (43.5%)	31 (44.8%)	35 (42.1%)	51 (43.6%)	
21-30	104 (38.5%)	30 (38.9%)	32 (39.5%)	42 (35.6%)	
31-40	17(7.5%)	3 (5.7%)	6 (8.3%)	8 (10.6%)	
Corticosteroids use, n (%)	210 (79.8%)	82(80.4%)	66(79.4%)	62(79.6%)	0.86
Co morbidity, n (%)					
Diabetes	90(34.2%)	3(2.5%)	9(10.9%)	78(86.6%)	<0.01
Hypertension	105 (39.9%)	31(30.4%)	34 (40.6%)	40 (51.6%)	<0.01
Cardiovascular diseases	150 (57.0%)	48 (46.6%)	47 (57.6%)	55 (70.1%)	<0.01

RESULTS

Table 2 MCRA showing the correlation between HbA1c levels and the risk of the development of next severe episode of COPD

	Hazard ratio	95% Confidence interval	p-value
HbA1c level			
<5.7%	1.21	0.89-1.62	0.78
5.7–6.4%	2.37	1.53–3.23	<0.01
≥6.5%	2.46	1.57–4.21	<0.01
Age, years	1.02	0.97-1.04	0.61
Gender, n (%)			
Male	1.20	0.80–1.80	0.38
Female	0.94	0.87–1.02	0.13
Smoking status, n (%)			
Never-smoker	1.18	0.78–1.78	0.43
Ex-smoker	1.09	0.66-1.81	0.73
Smoker	1.28	0.72-1.33	0.21
COPD duration in years			
<3 years	0.91	0.67-1.42	0.69
3-5 years	1.01	0.97-1.12	0.59
>5 years	1.18	0.73-1.78	0.46
Number of admissions in last year			
<2	3.13	2.64-4.35	<0.01
>2	1.25	0.83–1.78	0.34
GOLD stage, n (%)			
Stage 1	1.27	0.78–1.82	0.39
Stage 2	1.32	0.69–2.42	0.68
Stage 3	0.97	0.64–1.74	0.76
Stage 4	0.76	0.46–1.51	0.64
CAT score, n (%)			
0-10	0.83	0.48–1.43	0.50
11-20	0.82	0.46–1.46	0.50
21-30	0.73	0.29–1.81	0.50
31-40	1.13	0.80–1.61	0.50
Corticosteroids use, n (%)	1.13	0.73–1.77	0.59
Comorbidity, n (%)			
Hypertension	1.13	0.80–1.61	0.50
Cardiovascular diseases	1.10	0.77–1.57	0.60

The clinical characteristics of study participants are depicted in Table 1. It was observed that patients who have higher body mass index also have high or moderate HbA1c levels when compared to patients with low HbA1c levels on the American diabetic association scoring (P<0.01).

The percentages of sufferers requiring ≥2 hospitalizations due to severe exacerbations in the past year associated with co-morbidities were significantly higher in patients with elevated HbA1c levels than those with low HbA1c levels (P<0.05). There were no statistically significant Differences were observed in the socio-demographic and clinical variables among the 3groups of study sample. (P>0.05). During subsequent follow up of study participants a total of seventy one had developed one or more episodes of severe exacerbations. Number of patients who had suffered from acute illness was higher in patients having elevated HbA1c levels (P<0.01). 39.3% of participants having high HbA1c and 32.5% of patients having moderate HbA1c levels developed acute illness when compared to those patients having low HbA1c levels (28.2%). Table 2 depicts the results of the correlation between HbA1c levels and the risk of developing the next severe episode of COPD by Multivariate Cox proportional hazards regression analysis. After eliminating confounding factors, it was observed that participants who are having high HbA1c level (HR=2.46, 95% CI: 1.57– 4.21; P<0.01) and moderate HbA1c level (HR=2.37, 95% CI: 1.53-3.23; P<0.01) were significantly associated with the risk of the next severe exacerbation compared with low HbA1c level.

To find out the role of hyperglycemia and causation of next acute exacerbation of COPD, analysis was conducted among subgroups which revealed that higher the values of HbA1c contributing to more severe development of acute illness in future among all sub groups, which was statistically significant at P<0.05 level was observed in study participants (table 3)

DISCUSSION

In our study, we found higher percentage of sufferers developing acute exacerbation was seen among 39.3% patients with high HbA1c, 32.5% in moderate HbA1c and 28.2% in low HbA1c study population. Majority of the existing studies reported that patients with established diagnosis of COPD with diabetes mellitus having moderate to higher HbA1c as per American diabetic association scoring are having more chances of developing future acute exacerbations when compared to lower HbA1c levels and the general population at large [12]. When compared to general population COPD patients are vulnerable to develop diabetes and also have worse control on glycemic

levels [13]. Hyperglycemic states always promote growth of infection causing organisms throughout body including airways and presence of high blood sugars in COPD patients results in poor control of infection in body leading to repetitive exacerbations and death in COPD patients [14]. In a prospective, observational study done by Figueira Goncalves JM et al with a maximum follow-up of 18 months, the presence of diabetes mellitus increased the risk of hospital admission due to COPD exacerbations was detected (OR=2.64, 95% CI: 1.09–6.56; *P*=0.033) the results of that study are similar to our study [9].

Table 3 MCRA of the Association of HbA1c Levels and the Risk of Next Exacerbation among Participants of the Different GOLD Stages and Diabetes

	HbA1c Level	Hazard ratio	95% Confidence interval	p-value
GOLD stages				
Stage 1–2 (n=84)	<5.7%	Index range		
	5.7–6.4%	2.42	1.12–4.47	0.04
	≥6.5%	2.87	1.29–6.17	0.02
Stage 3 (n=122)	<5.7%	Index range		
	5.7–6.4%	1.79	1.18–3.64	0.03
	≥6.5%	2.32	1.06–4.52	0.03
Stage 4 (n=57)	<5.7%	Index range		
	5.7–6.4%	2.34	1.23–8.16	0.02
	≥6.5%	3.90	1.35–12.9	0.04
Diabetes status				
Diabetes (n=90)	HbA1c as a continuous variable	1.73	1.14–3.39	0.01
Non-Diabetes (n=173)	HbA1c as a continuous variable	1.58	1.05–2.38	0.03

Another prospective cohort study indicated that COPD patients with diabetes were significantly associated with a higher risk of death (OR=3.38, 95% CI: 1.08–13.89; P=0.037) [8]. Though the affiliation of diabetes with intense exacerbation in COPD has been adequately established, the connection between hyperglycemia and detrimental final results after COPD remains controversial. Our outcomes are in evaluation with a preceding study, [15] wherein the Cox regression evaluation confirmed that the ranges of HbA1c on admission had been no longer a predictor neither of the time to the next moderate or severe COPD exacerbation (HR=1.00, 95% CI: 0.80–1.25; P=0.98) nor of the time to the following severe COPD exacerbation (HR=0.90, 95% CI: 0.74–1.33; P=0.96). In addition, HbA1c on admission was not a predictor of mortality (HR=0.97, 95% CI: 0.59–1.58; P=0.9).

CONCLUSION

Hyperglycemia and poor glycemic control are associated with subsequent acute exacerbations in patients diagnosed with COPD. However, further research is required to confirm this by adding more confounders in future studies.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Kakumanu Kalyani collected data, interpreted the statistical values. She along with Chappidi Rajesh Reddy designed the study and contributed in drafting and editing the manuscript. Muthineni Manoj Kumar contributed in manuscript writing and processing the collected data. He also contributed in compiling the data, interpretation of data and wrote final draft of manuscript, which was read and approved by all authors.

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