Diabetes mellitus in acute exacerbation of chronic obstructive pulmonary disease – the tip of the iceberg

Devika Tayal,[1] Prerna Jain,[1] Mamta Bhardwaj,[2] Amit Sharma[2]

[1]Department of Biochemistry, National Institute of Tuberculosis and Respiratory Disease, New Delhi; [2]Department of Tuberculosis and Respiratory Disease, National Institute of Tuberculosis and Respiratory Disease, New Delhi, India

Correspondence: Amit Sharma, Department of Tuberculosis and Respiratory Disease, National Institute of Tuberculosis and Respiratory Disease, Rm No. 208, Second Floor, OPD Building, New Delhi 110030, India.
E-mail: dramitsharma55@yahoo.co.in

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Informed consent: written informed consent was obtained from all participants before study enrollment.

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Abstract

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by systemic inflammation caused primarily by tobacco use, and it is associated with an increased susceptibility to respiratory infections, both viral and bacterial, which are responsible for acute COPD exacerbations (AECOPD). Diabetes mellitus is one of the most common comorbidities in COPD patients. In our study, we attempted to detect previously undiagnosed diabetes in AECOPD patients who presented to our institute. The study included 100 patients who had been diagnosed with AECOPD. Pearson's coefficient correlation analysis was used to assess the relationship between various parameters. The vast majority of patients belonged to group 3 (diagnosed at the time of admission as having type 2 diabetes). Glycosylated hemoglobin (HbA1c) had a significant positive correlation with body mass index, cholesterol, and total leukocyte count but a negative correlation with oxygen saturation. Using HbA1C, nearly two-thirds of the AECOPD were newly diagnosed with diabetes mellitus. Our findings suggest that diabetes is significantly underdiagnosed in COPD patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is an incompletely reversible airway obstruction. It is one of the major causes of morbidity and mortality worldwide. It is a growing healthcare problem that is expected to deteriorate with the increase in the age of patients and the use of tobacco products. It includes obstruction of small airways known as chronic obstructive bronchitis and air trapping with shortness of breath in response to physical exertion known as emphysema. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to toxic particles or gases. COPD involves accelerated aging of the lungs and abnormal repair driven possibly by oxidative stress [1]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) was launched in 1997, as a collaboration of the National Heart, Lung, and Blood Institute, the National Institutes of Health, and the World Health Organization to increase awareness of COPD, to disseminate causes of COPD and issue management guidelines [2]. Although tobacco smoking is the principal risk factor for COPD, occupational and environmental exposures to chemical fumes, dust, and other lung irritants are also responsible for

COPD [3]. Previous episodes of either severe lung infections or pneumonia in childhood increase the risk for the development of COPD in future periods of life in those individuals [4]. Acute exacerbations in COPD (AECOPD) are characterized by worsening of underlying chronic inflammation of the airways and can be attributed to disease progression. These exacerbations are mainly triggered by viral or bacterial infections which are further linked to poor prognosis of COPD patients. Frequent exacerbations are associated with increased mortality, decline in lung function, and quality of life [5].

COPD is associated with various comorbidities and severity increases with age, which can adversely affect health status and complicate management of COPD patients. Approximately 80% of COPD patients have at least one comorbidity. Studies have shown that COPD is associated not only with other respiratory diseases like pneumonia but also with diseases affecting other organ systems, such as the musculoskeletal system (osteoporosis), cardiovascular system (angina), metabolic syndromes, diabetes, and neurological (anxiety/ depression) [6]. The results of the logistic analysis performed in the Iranian population showed that the probability of having chronic respiratory and pulmonary diseases was 2.12 times, diabetes mellitus was 1.54 times, cardiovascular comorbidities was 1.52 times and hypertension was 1.43 times higher in COPD patients in comparison to general population. Diabetes is one of the most common comorbidities among COPD patients [7]. Localized lung inflammation can give rise to systemic inflammation with the aid of inflammatory molecules and factors that are involved in the pathogenesis of common comorbidity, *i.e.*, diabetes mellitus. Therefore, parameters that are either source or affected in systemic inflammation were assessed in the present cohort of COPD patients to delineate plausible mechanisms of interaction among various variables and glycosylated hemoglobin (HbA1c).

Materials and Methods

Study design and patient criteria

The study enrolled a total of 100 patients with AECOPD who presented to the Respiratory Medicine Outpatient Department (OPD) of the institute (Table 1). Our hospital is a tertiary care center for respiratory diseases and a large number of patients of AECOPD present to the hospital for treatment. Patients between the ages of 40-70 years were included. These patients were diagnosed with AECOPD according to Anthonisen criteria. Patients who were diagnosed with COPD, within 5 years of the present study were included. Prior to enrolment, patients were not diagnosed as having diabetes mellitus. The patients with AECOPD included in the present study were diagnosed with diabetes mellitus at the time of their first visit to the hospital during the routine blood investigations. Patients with chronic lung disease other than COPD and with a previous history of pulmonary tuberculosis were not included in the current study. Patients with chronic liver disease, renal disease, and HIV were also excluded. Patients taking treatment for diabetes mellitus or having any other comorbid conditions were excluded from the study. This study was approved by the ethical board of the institute.

Statistical analysis

All the statistical analysis was performed using GraphPad Prism 9. For normally distributed data, Pearson correlation analysis was used to obtain a correlation coefficient among HbA1c and other parameters of the study (Table 2). A $p<0.05$ was considered statistically significant (two-tailed).

Table 1. Demographic profile of study participants.

Number of study participants		Age (in years) (mean age ± SD)
Total (n=100)		57.8±7.65
Male (n=73)		58.2±7.44
Female (n=23)		56.6±8.2
HbA1c groups (gender)		
Group 1 (HbA1c <5.7%)	Male (n=2)	46±5.65
	Female (n=0)	-
Group 2 (HbA1c 5.7-6.4%)	Male (n=22)	57±7.53
	Female (n=8)	52.87±7.27
Group 3 (HbA1c ≥6.5%)	Male (n=49)	59.34±7.02
	Female (n=19)	58.15±8.26

SD, standard deviation; HbA1c, glycosylated hemoglobin.

Table 2. Pearson's correlation analysis in chronic obstructive pulmonary disease patients.

Parameters	Pearson's coefficient (r)	p
Body mass index *vs.* cholesterol	0.5	0.00000011*
HbA1c *vs.* body mass index	0.29	0.003*
HbA1c *vs.*cholesterol	0.29	0.003*
HbA1c *vs.*SpO2	-0.29	0.0029*
HbA1c *vs.*TLC	0.27	0.0049*
HbA1c *vs.*ABG-pH	-0.13	0.18
HbA1c *vs.*ABG-pO2	-0.20	0.043*
HbA1c *vs.*ABG-pCO2	0.15	0.12
HbA1c *vs.* duration of hospital stay (days)	0.38	0.00029*
RBS vs duration of hospital stay (days)	0.349	0.0008*

HbA1c, glycosylated hemoglobin; SpO2, oxygen saturation; TLC, total leukocyte count; ABG, arterial blood gas; pO2, partial pressure of O2; pCO2, partial pressure of CO2; RBS, random blood sugar; *p-value is less than 0.05.

Results

A total of 100 patients with AECOPD were recruited in the present study. It was observed that the average age of the participants in the study was 57.8 years (95% confidence interval: 56.3 to 59.3). Among these participants, there were more male COPD patients (73 individuals) with an average age of 58.2 years. The mean age of female COPD patients (n=27) was 56.6 years. Among the patients grouped into three groups according to HbA1c levels, 49 males and 19 females were observed in group 3 (HbA1c≥6.5%), 22 males and 8 females in group 2 (HbA1c=5.7-6.4%) and only 2 males were present in group 1 (HbA1c<5.7%).

Blood samples collected from the patients were subjected to various biochemical and hematological tests. These diagnostic tests assisted pulmonologists in planning essential treatment for patients. In the present cohort of subjects, patients were categorized into three groups according to HbA1c levels. Among 100 COPD individuals, there were 68% of patients with HbA1c more than 6.5% (group 3). 30% of patients were pre-diabetic with HbA1c ranging between 5.7-6.4% (group 2) and 2% of the total population had normal HbA1c levels (group 1). Patients with AECOPD in all three groups were hospitalized for appropriate treatment to manage the severity of the disease. However, it was observed that patients in group 3 (HbA1c≥6.5%) had a prolonged duration of hospital stay in comparison to the other two groups. Duration of hospital stays for patients positively correlated with r=0.38 (p=0.00029) with levels of HbA1c. Various blood tests were performed on these patients, the results of which were then correlated with HbA1C levels.

Correlation of glycosylated hemoglobin with body mass index and cholesterol levels

Metabolic syndrome is a common extrapulmonary comorbidity in patients with COPD. In type 2 diabetes, a higher body mass index (BMI) is associated with high HbA1c. Out of 100 COPD patients included in this study, 43% of patients were overweight/pre-obese (BMI=25-29.99kg/cm^2), whereas 2% were observed to be obese (BMI≥30kg/cm^2). The weight of 52% of the patients was in the range of appropriate weight (BMI=18.5-24.99kg/cm^2), while 3% of the population was underweight (BMI<18.5kg/cm^2). We observed a significant moderately positive correlation among these parameters with r=0.29 (p=0.003). The Pearson correlation for BMI has been depicted in Figure 1A. The average cholesterol level of 100 COPD patients in the present study was 187.015±20.72. An association of increasing BMI with higher cholesterol is well established, we also observed a significantly positive correlation among them (r=0.5). We also observed a significant association between HbA1c and BMI. Correlation analysis performed for HbA1c and cholesterol revealed a moderately positive (r=0.29) association between these parameters, which was highly significant (p=0.003) (Figure 1B). These noteworthy associations indicate the role of obesity in determining the severity of COPD patients due to disorders existing simultaneously.

Total leukocyte count in chronic obstructive pulmonary disease patients and its association with glycosylated hemoglobin

Elevated levels of leukocyte count in COPD generally indicate a bacterial infection. The AECOPD in which HbA1c is raised are more frequently associated with *Pseudomonas aeruginosa*. In the present study, authors also observed *P. aeruginosa* as the most common pathogen being isolated from AECOPD patients having high glycemic index. Approximately 68% of the total study population had a total leukocyte count (TLC) above the normal reference range with a significant mild correlation between TLC and HbA1c (r=0.278, p=0.0049) (Figure 2).

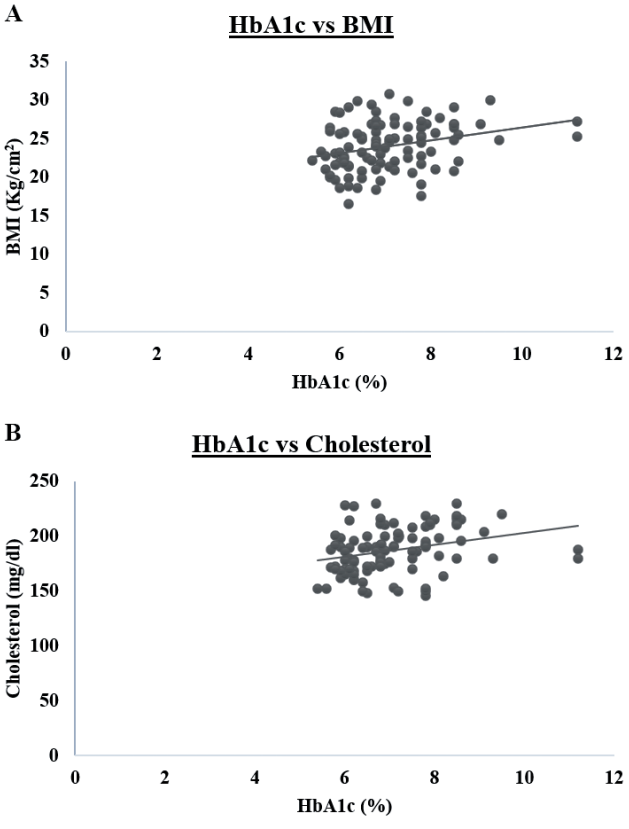

Figure 1. Association of metabolic parameters in chronic obstructive pulmonary disease patients. Calculated (A) body mass index (BMI) and (B) serum cholesterol levels were employed for Pearson's correlation analysis with glycosylated hemoglobin (HbA1c); a p-value lower than 0.05 was considered significant.

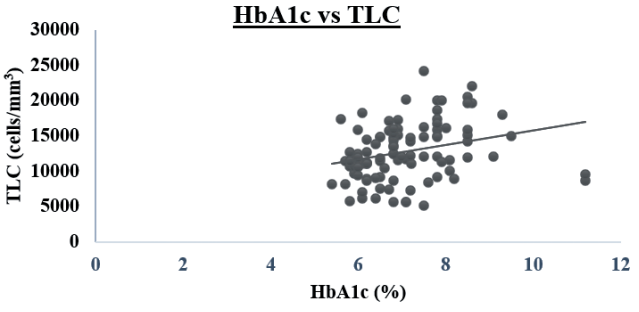

Figure 2. Association of total leukocyte count with glycosylated hemoglobin (HbA1c) in chronic obstructive pulmonary disease (COPD) patients. Hematological tests were performed routinely in COPD patients. The TLC count of these patients was used to find a relation with HbA1c using Pearson's coefficient analysis; p-values lower than 0.05 were considered significant.

Effect of glycosylated hemoglobin on peripheral oxygen levels and arterial blood gas parameters

The study revealed that 79% of total COPD patients had saturation levels of less than 84%. Only 3% of the population had an oxygen saturation (SpO_2) of more than 90%. SpO_2 levels were observed to decrease with an increase in HbA1c (%). Pearson's coefficient r is -0.29 (p=0.002) (Figure 3). Positive correlation of partial pressure of CO_2 in arterial blood gas (ABG) analysis with HbA1c was not significant (r=0.15, p=0.12) (Table 2). Partial pressure of CO_2 was higher in group 3 patients with HbA1c≥6.5%, as compared to other groups. Consequently, this indicates an increased probability of respiratory failure. Therefore, a negative correlation of HbA1c with SpO_2 and ABG analysis results demonstrated deterioration in lung function. In the present cohort of subjects, 50% of total patients had respiratory acidosis, 24% of patients had respiratory acidosis with metabolic alkalosis, 2% of the population had respiratory alkalosis whereas 1% had metabolic acidosis. On the other hand, mixed acidosis was present in 6% of the total population.

Effect of glycosylated hemoglobin on the severity of chronic obstructive pulmonary disease patients

The study participants were grouped into three groups depending on their random blood sugar (RBS) at the time of admission. The first group had RBS<140 mg/dL, the second group had RBS in the range of 140-200 mg/dL and the last group included patients with RBS>200 mg/dL. It was observed that patients with RBS>200mg/dL had a more severe form of AECOPD than other groups. Correspondingly, these patients belonged to group 3 with higher HbA1c (≥6.5%), thus higher HbA1c correlates with a severe form of AECOPD. Moreover, patients with more severe exacerbations of COPD require intensive care and a longer duration of treatment. However, patients with higher RBS at the time of admission and HbA1c≥6.5% required more days of treatment. Duration of hospital stay for patients positively correlated with r=0.38 (p=0.00029) with levels of HbA1c. Similarly, RBS at the time of admission positively correlated with the duration of hospital stay (r=0.349, p=0.008). Hence, it is proven that the severity of exacerbations in COPD patients was greatly affected by glycemic index. It is, therefore, essential to consider these parameters for predicting and monitoring patient's health in the hospital.

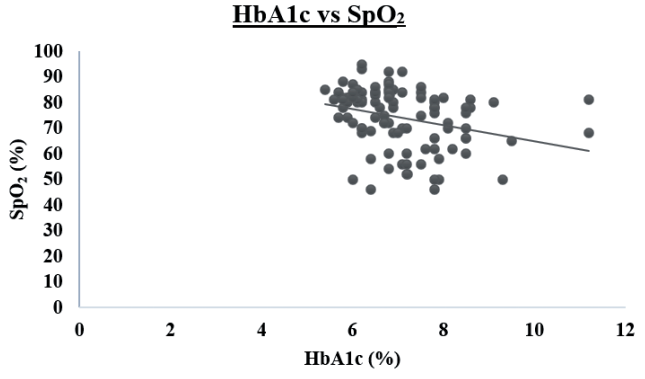

Figure 3. Association of glycosylated hemoglobin (HbA1c) with oxygen saturation (SpO_2) levels and arterial blood gas parameters in chronic obstructive pulmonary disease (COPD) patients. Peripheral SpO_2 level is a crucial parameter to be monitored in COPD individuals. SpO_2 levels were correlated with HbA1c using Pearson's analysis; a p-value lower than 0.05 was considered significant.

Discussion

COPD is known to be associated notably with many important chronic co-morbid diseases including hypertension, cardiovascular disease, obstructive sleep apnea, and type-II diabetes mellitus. The present study has revealed that type 2 diabetes is the tip of the iceberg in COPD patients. Our institute is a tertiary care center for respiratory diseases, and a large number of patients suffering from AECOPD visit the OPD of the institute. Several blood biomarkers are assessed in these AECOPD patients to monitor their health status. The patients of AECOPD are under stress that releases sympathomimetic hormones and endogenous steroids which may cause transient dysglycemia. Hence, an increased blood sugar level taken at this time would not reflect the true picture of the glycemic status of the COPD patient. Therefore, HbA1c is an important indicator of a patient's glycemic status averaged over 3 months and is also a diagnostic tool [8]. HbA1c is a validated measure that is characterized by lower biological variability. Measurement of HbA1c at the time of diagnosis of AECOPD is unlikely to be affected significantly by the physiological stress of an AECOPD. The results of our study prove beyond doubt that type 2 diabetes is a very common undiagnosed comorbidity in COPD (68%) and every COPD patient should be actively screened for the presence of diabetes mellitus.

We also observed that the level of increased hyperglycemia (as seen with increased levels of HbA1c) is associated with a worsening level of AECOPD. This further intensifies the fact that the higher the blood sugar level in the patient, the more severe the attack of AECOPD. The correlation of AECOPD with hyperglycemia has been documented in past studies as well [9,10]. However, the correlation of the severity of AECOPD with increased HbA1c levels has not been consistently demonstrated before in the Indian population. The present study showed that patients with HbA1c≥6.4% suffered from more severe exacerbations of COPD. Another study revealed COPD patients are at higher risk of developing type 2 diabetes as compared to the general population, and this risk is enhanced with disease severity. Increased glucose concentration can stimulate bacterial growth and promote the interaction of bacteria with airway epithelia [10]. A previous study demonstrated that AECOPD with high HbA1c were commonly associated with *P. aeruginosa* [11]. Similarly, we also observed that *P. aeruginosa* was obtained in the sputum culture of AECOPD patients with high glycemic index.

There is documentary evidence to show that lung function and hyperglycemia are inversely co-related [12]. A significant decline in dynamic lung volumes [forced vital capacity (FVC), forced expiratory volume in the first second (FeV_1)] in patients with type 2 diabetes has been shown by Mondal *et al*. [13], and by Tai *et al.* [14]. Type 2 diabetes influences the progression and prognosis of COPD due to direct effects of hyperglycemia on lung physiology, including glycosylation of connective tissues, reduced pulmonary elastic recoil, increased muscle weakness, and inflammation [15]. The Fremantle Diabetes Study demonstrated that with every 1% increase in HbA1c levels, FVC declines by 4% of the predicted value [16].

Our study was a prospective study that clearly demonstrated that the poorer the glucose control, the more severe the exacerbation of COPD. Another recent study has demonstrated that the percentage of HbA1c was associated with exacerbation of COPD,

with HbA1c being a good predictor of disease severity in patients with COPD [17]. A non-linear association was observed between HbA1c and FEV_1 in diabetic patients with good glucose control as compared to patients with poor glucose control. Therefore, pulmonary function may improve from a stringent glycemic target [18]. The findings by Maan *et al*. 2021 concluded that high HbA1c or poor glucose control impairs lung functions in type 2 diabetes. They have also shown that uncontrolled diabetes is more damaging to lung functions compared to the duration of diabetes [12].

Our study had some limitations. The number of patients was not very large (100 patients). The study only revealed a very high association of AECOPD with undiagnosed diabetes but did not assess the pre-AECOPD period of the patient especially any drug history particularly oral steroids and any history of recent exacerbation within the preceding 3 months.

Conclusions

The results of the present study elucidate a feasible mechanism *via* which COPD is delineated as a systemic inflammatory disease also affecting the glucose homeostasis reflected in the high HbA1C in COPD patients hitherto undiagnosed with diabetes mellitus. Elevated levels of HbA1C are responsible for the decline in lung function, and we have presented some evidence that the degree of poor glucose control correlates with the severity of COPD. This may establish more emphasis on the early diagnosis of DM in such patients. Good glycemic control may improve the level of COPD severity. However, we need larger trials to firmly establish these associations and their co-relation.

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