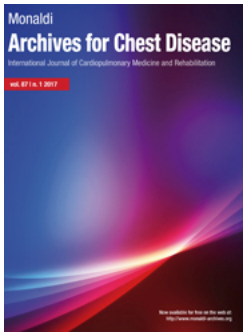

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Diabetes mellitus in acute exacerbation of chronic obstructive pulmonary disease – the tip of the iceberg

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Ethical Approval and Consent for participation: This study was approved by Institute Ethics Committee with reference number as NITRD/PGEC/2018/6621. All the patients were recruited in the study only after obtaining proper consent from the patients or their representatives.

Availability of data and materials: The raw data used and analysis presented in the current study will be available with corresponding author.

Abstract

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 co-morbidities 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 II diabetes). HbA1c had a significant positive correlation with BMI, cholesterol, and TLC, but a negative correlation with SpO_2. 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.

Key words: co-morbidity; systemic; inflammation; metabolic syndrome; respiratory.

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 which is expected to deteriorate with increase in age of patients and 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 ageing of 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, dusts, and other lung irritants are also responsible for COPD [3]. Previous episodes of either severe lung infections or pneumonia in childhood increases the risk for development of COPD in future period 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 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 were 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 aid of inflammatory molecules and factors which are itself involved in pathogenesis of common comorbidity i.e., diabetes mellitus. Therefore, parameters which are either source or effected in systemic inflammation were assessed in the present

cohort of COPD patients to delineate plausible mechanism of interaction among various variables and HbA1c.

Materials and Methods

Study design and patient criteria

The study enrolled a total of 100 COPD patients in acute exacerbations who presented to the Respiratory Medicine OPD of the institute. Our hospital is a tertiary care centre for respiratory diseases and large number of patients of AECOPD present to the hospital for treatment. Patients within age of 40-70 years were included. These patients were diagnosed as acute exacerbation of COPD according to Anthonisen criteria. Patients who were diagnosed as COPD, within 5 years of 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 first visit in the hospital during the routine blood investigations. Patients with chronic lung disease other than COPD and with previous history of pulmonary TB 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 co-morbid conditions were excluded from the study. This study was approved by ethical board of institute.

Statistical analysis

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

Results

Total 100 COPD patients in acute exacerbation were recruited in the present study. It was observed that the average age of the participants in the study was 57.8 years (95% CI: 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 haematological tests. These diagnostic tests assisted pulmonologist in planning essential treatment for patients. In the present cohort of subjects, patients were categorized in to 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 total population had normal HbA1c levels (group 1). Patients with AECOPD in all three groups were hospitalized for appropriate treatment to manage severity of disease. However, it was observed that patients in group 3 (HbA1c ≥6.5%) had prolonged duration of hospital stay in comparison to other two groups. Duration of hospital stay for patients positively correlated with r=0.38 (p value: 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 HbA1c with body mass index and cholesterol levels

Metabolic syndrome is a common extrapulmonary co-morbidity in patients with COPD. In type II diabetes, higher body mass index (BMI) is associated with high HbA1c. Out of 100 COPD patients included in this study, 43% of patients were over-weight/ pre-obese (BMI= 25-29.99kg/cm^2), whereas 2% were observed to be obese (BMI≥30kg/cm^2). Weight of 52% of patients were in range of appropriate weight (BMI=18.5-24.99kg/cm^2), while 3% population was underweighted (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. Average cholesterol level of 100 COPD patients in present study was 187.015 ± 20.72. An association of increasing BMI with higher cholesterol is well established, we also observed significantly positive correlation among them (r=0.5). We also observed 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 role of obesity in determining severity of COPD patients due to disorders existing simultaneously

Total leukocyte count in COPD patients and its association with HbA1c

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

Effect of HbA1c on peripheral oxygen levels and arterial blood gas parameters

79% of total COPD patients had saturation levels less than 84%. Only 3% of population had SpO_2 more than 90%. SpO_2 levels were observed to decrease with increase in HbA1c (%). Pearson's coefficient r is -0.29 (p=0.002, Figure 3A). Positive correlation of pCO_2 in arterial blood gas (ABG) analysis with HbA1c was not significant (r= 0.15, p=0.12), partial pressure of CO_2 was higher in group 3 patients with HbA1c ≥6.5% as compared to other groups. Consequently, indicating increased probability of respiratory failure. Therefore, 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 population had respiratory alkalosis whereas 1% had metabolic acidosis. On the other hand, mixed acidosis was present in 6% of total population.

Effect of HbA1c on severity of COPD patients

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

Discussion

COPD is known to be associated notably with many important chronic co-morbid diseases including hypertension, cardiovascular disease, obstructive sleep apnoea and type-II diabetes mellitus. The present study has revealed that type II diabetes is the tip of the iceberg in COPD patients. Our institute is a tertiary care centre for respiratory diseases, and large number of patients suffering from AECOPD visit OPD of the institute. Several blood biomarkers are assessed in these AECOPD patients to monitor their health status. The patients of AECOPD are in a stress which 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 glycaemic status of the COPD patient. Therefore, Glycosylated Haemoglobin (HbA1c) is an important indicator of a patient's glycaemic status averaged over three months and is also a diagnostic tool [8]. HbA1c is a validated measure that is characterised 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 II diabetes is a very common undiagnosed co-morbidity in COPD (68%) and every patient of COPD should be actively screened for the presence of diabetes mellitus.

We also observed that the level of increased hyper glycemia (as seen with increased levels of HbA1c) is associated with a worsening level of AECOPD. This further intensifies the fact that, higher the blood sugar level in the patient, more severe is the attack of AECOPD. The co-relation of AECOPD with hyper glycemia has been documented in past studies as well [9, 10,16]. However, the co-relation of severity of AECOPD with increased HbA1c levels has not been consistently demonstrated before in Indian population. Present study showed that patients with HbA1c $\geq$ 6.4% suffered with more severe exacerbations of COPD. Another study revealed COPD patients are at higher risk of developing type II diabetes as compared to general population and this risk enhances with disease severity. Increased glucose concentration can stimulate bacterial growth and promote interaction of bacteria with airways epithelia [10]. A previous study demonstrated that AECOPD exacerbations with high HbA1c were commonly associated with *P. aeruginosa* [11]. Similarly, we also observed that *P. aeruginosa* was obtained in sputum culture of AECOPD patients having high glycaemic index.

There is documentary evidence to show that lung function and hyper glycemia are inversely co-related [12]. A significant decline in dynamic lung volumes (FVC, FeV_1) in patients of type 2 diabetes has been shown by Mondal et al. [13] and by Tai et al. [14]. Type II diabetes influences the progression and prognosis of COPD due to direct effects of hyperglycaemia 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 decline by 4% of predicted value [16].

Our study was a prospective study which clearly demonstrated that poorer is the glucose control, more severe is the exacerbation of COPD. Another recent study has demonstrated that 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 glycaemic target [18]. The findings of Maan et al's. 2021 study concluded that high HbA1c or poor glucose control impairs lung functions in type II diabetes. They had also shown that uncontrolled diabetes is more damaging to lung functions compared to 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 three months.

Conclusions

The results of present study elucidate a feasible mechanism via which COPD is delineated as systemic inflammatory disease also affecting the glucose homeostasis reflected in the high HbA1C in COPD patients hitherto undiagnosed with diabetes mellitus. Elevated levels of glycated Hb are responsible for decline in lung function and we have presented some evidence that the degree of poor glucose control correlates with the severity of the COPD. This may establish more emphasis on the early diagnosis of DM in such patients. Good glycaemic 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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Table 1. Demographic profile of study participants

Number of study participants		**Age (in years) (mean age ± SD)**
Total (n=100)		57.8 ±
Male (n=73)		58.2 ±
Female (n=23)		56.6 ±
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

Table 2. Pearson's correlation analysis in COPD patients.

Parameters	**Pearson's coefficient (r)**	**p-value**
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 SpO_2	-0.29	0.0029*
HbA1c vs TLC	0.27	0.0049*
HbA1c vs ABG-pH	-0.13	0.18
HbA1c vs ABG-pO_2	-0.20	0.043*
HbA1c vs ABG-pCO_2	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*

*p-value is less than 0.05.

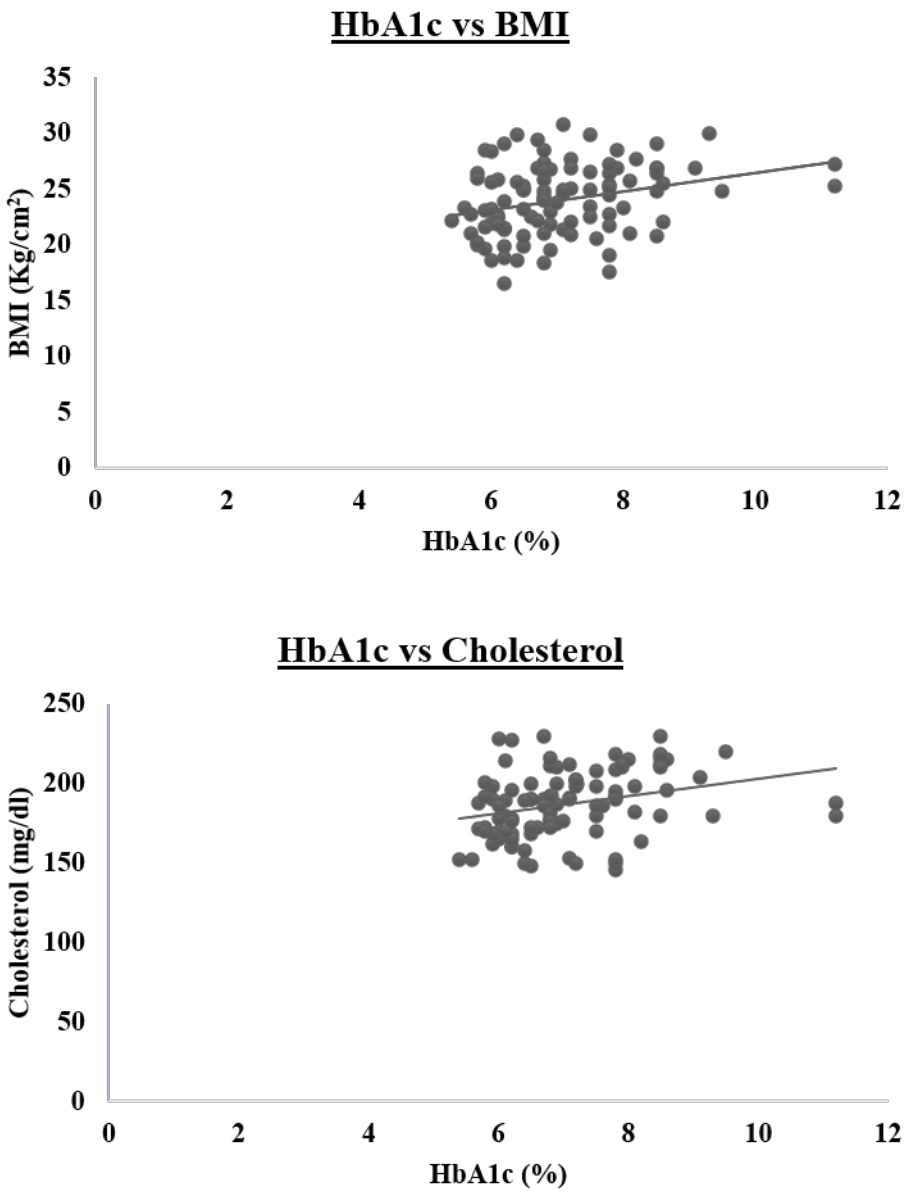

Figure 1. Association of metabolic parameters in COPD patients. Calculated (A) BMI and (B) serum cholesterol levels were employed for Pearson's correlation analysis with HbA1c; p-value less than 0.05 was considered as significant.

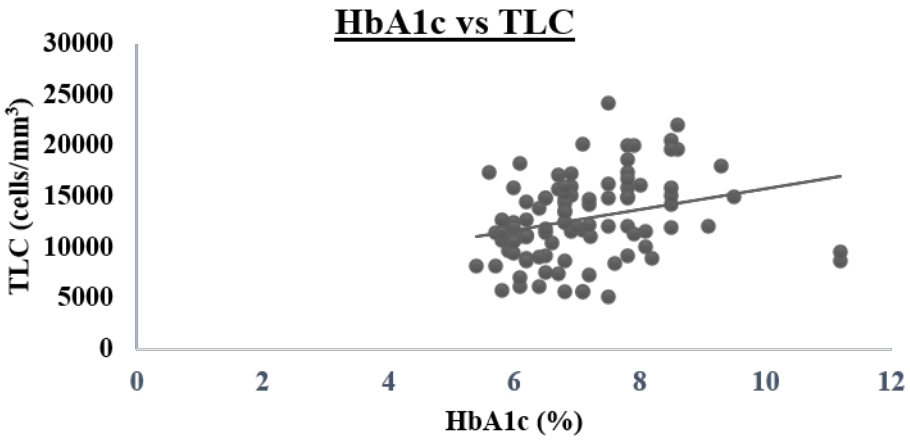

Figure 2. Association of TLC count with HbA1c in COPD patients. Haematological tests were performed routinely in COPD patients. TLC count of these patients was used to find relation with HbA1c using Pearson's coefficient analysis. p-values less than 0.05 were considered as significant.

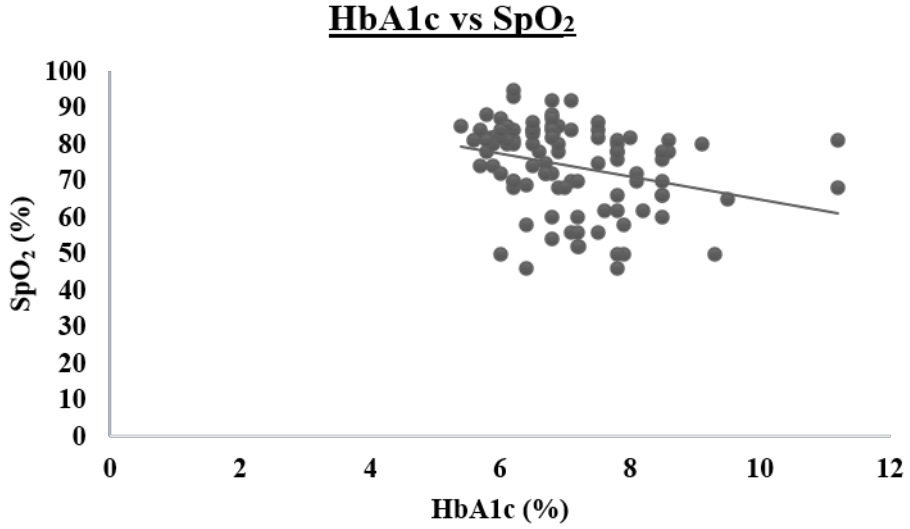

Fig 3: Association of HbA1c with SpO_2 levels and ABG parameters in COPD patients. Peripheral oxygen saturation level is crucial parameter to be monitored in COPD individuals. SpO_2 levels were correlated with HbA1c using Pearson's analysis. p value less than 0.05 were considered significant.