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Research Article

Impact of Poor Glycemic Control on Severity and Clinical Course of Chronic Obstructive Pulmonary Disease in Patients With Co Existing Type 2 Diabetes Mellitus - One Year Prospective Study

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) and type 2 Diabetes Mellitus (DM) are common and under diagnosed chronic non-communicable medical conditions in India. The escalating epidemic of DM is a great challenge for the clinicians treating COPD as large number of patients have Poor Glycemic Control (PGC). We undertook this trial to study the influence of PGC on severity and disease outcome in COPD subjects with concomitant DM.

Materials and methods: COPD patients either known or newly diagnosed DM cases as per WHO criteria were enrolled in the study and grouped into patients with PGC and Optimal Glycemic Control (OGC) based on HbA1c measurements. Subjects were closely monitored for 1 year.

Results: Of the 490 subjects analyzed, 336 (68.57%) had PGC and 154 (31.43%) had OGC. COPD patients with PGC had more severe disease compared to OGC (Mean FEV1% predicted 48.47 ± 13.7 *vs* 67.4 ± 13.86, p= 0.0061) and also DOSE score (4.35 ± 1.88 *vs* 3.18 ± 2.30 p= 0.0052) at the baseline. After 1 year, patients with PGC had statistically significant high rates of exacerbations. The mean DOSE scores were statistically greater in PGC patients after 12 months suggesting worsening of COPD symptoms and quality of life. Hospitalization was significantly frequent and longer in PGC patients. (6.56 ± 1.70 *vs* 4.16 ± 1.26 p= 0.0004).

Conclusion: Patients with PGC had more severe COPD, poor lung function, high symptom score, and increased risk of exacerbations with frequent and prolonged hospitalizations.

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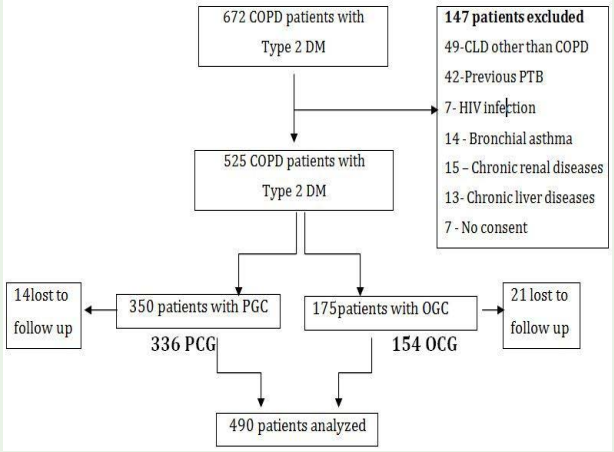
Introduction

Chronic Obstructive Pulmonary Disease (COPD) and type 2 diabetes mellitus (DM) are common and under diagnosed chronic non-communicable medical conditions in India. COPD is a progressive, partially reversible airflow obstructive disease and is a growing public health problem globally. In its advanced stage, the disease causes severe disabilities and poor quality of life [1-3]. It is predicted that by 2020 COPD will be the third leading cause of death worldwide with Asian countries having three times the number of patients than the rest of the world [4]. The largest number of deaths will be in the South East Asian region, where mortality due to COPD is estimated to grow by 160%, totaling more than the combined numbers of deaths due to malaria, tuberculosis and HIV/AIDS [5].

India is one of the largest countries in Asia with population of over 1.26 billion, where small increases in the percentage prevalence of a disease can translate into large increases in the number of cases. Crude estimates suggest, there are 30 million COPD patients in our country [6] India contributes significantly to the growing percentage of COPD mortality, which is estimated to be amongst the highest in the world; i.e. more than 64.7 estimated age standardized death rate per 1,00,000 in both sexes. This would translate to about 5,56,000 cases in India (>20%) out of a world total of 2,748,000 annually. Such mammoth volumes of disease have the potential to have devastating impact on the health systems and state economies [7,8]. If mortality due to comorbid conditions like DM associated with COPD are taken together, then the convergence of these two non-communicable chronic diseases pose a great impact on the outcome of the disease.

India is also diabetic capital of the world with approximately 65 million Indians having DM. Studies have demonstrated that the every fifth diabetic in the world is an Indian. Global burden of Diabetes Mellitus (DM) is increasing. In 2014 the global prevalence of DM was estimated to be 9% among adults [9]. WHO projects that diabetes will be the 7th leading cause of death in 2030 [10]. More than 80% of diabetes deaths occur in low- and middle-income countries. As per the



Flow chart 1: Inclusion of patients into the study.

International Diabetes Federation (2013), approximately 50% of all people with diabetes live in just three countries: China (98.4 million), India (65.1 million) and the USA (24.4 million). Hence India, the second most populous country of the world, has been severely affected by the global DM epidemic [11].

Significant proportions of these DM patients have poorly controlled diabetes in India. The Poor Glycemic Control (PGC) has substantial effect on the complications of DM. There is extensive body of evidence on the impact of PGC on various cardiovascular, renal, musculoskeletal, neurological and psychological diseases like depression [13]. However; studies linking PGC with COPD are scarce. Hence, we undertook this trial to study the influence of PGC on severity and disease outcome in COPD subjects with concomitant DM.

Materials and Methods

This was a prospective study of patients diagnosed with COPD as per Global Initiative for chronic obstructive lung disease (GOLD) 1 criteria 2013, carried out at the Inpatient and outpatient departments of Pulmonary medicine, Internal Medicine and Endocrinology sections at a tertiary care hospital between Jan 2012 to Dec 2013. Patients were enrolled in the study only if they have either known or newly diagnosed DM status.

Patients were excluded from the study if they had pulmonary conditions other than COPD (e.g. Bronchial Asthma, TB, HIV infection), connective tissue disorders, chronic renal failure, chronic liver disease, malignancies on long term steroid or cytotoxic drug therapy and chronic alcoholics.

Ethical clearance was obtained from the Institutional ethical review committee prior to commencement of the study. Baseline data was recorded which included age, sex, biomass fuel exposure, symptoms related to respiratory system and DM with duration of illness, level of dyspnea (Medical Research Council range (0-4), smoking status (current or nonsmoker or ex-smoker), pack years, current treatment, previous medications, occupation, and number of exacerbations, that is, emergency hospital admissions or unscheduled hospital visits in last 1-year. Also dyspnea score (D), level of airflow obstruction (O), current smoking status (S), and exacerbations (E) (DOSE) score were noted. Mortality has been found to be associated with patients with a DOSE index score >4 [13].

COPD diagnosis

All the participants were subjected to spirometry and patients with post bronchodilator FEV1/FVC less than 70% predicted were considered as cases of COPD. Then they were categorized as mild, moderate, severe and very severe COPD patients as per the GOLD guidelines [1].

DM diagnosis

Screening and diagnosis of DM followed national guidelines [14] and Fasting Blood Sugar (FBS) is used with cut-off thresholds in line with those recommended by WHO. In brief, FBS > 126 indicates DM and FBS<110 mg/dl is normal. The patients already known to have DM were directly enrolled in the study as "Known DM" cases with COPD. Patients whose diabetes status was uncertain underwent Random Blood Sugar (RBS) testing, and if was more than 126 mg/dl, the subjects were further assessed with FBS and Post Prandial Blood Sugar (PPBS). If FBS was more than 126 mg/dl or PPBS more than 200 mg/dl the subjects were confirmed as having DM after which they were classified as new DM cases with COPD. All the participants underwent glycosylated hemoglobin (HbA1c) evaluation and HbA1c >7 were classified as PGC and HbA1c <7 as Optimal Glycemic Control (OGC) [12].

Biomass Exposure- Biomass fuel exposure was defined as a lifetime exposure of 10 years or greater from the use of indoor fire using coal or coke; wood, crop residues or dung as the primary means of cooking or heating.

Both the groups PGC with COPD and OGC with COPD were closely monitored for 1 year every month for symptoms, exacerbations, severity, hospital stay and mortality related to COPD.

Statistical Analysis

Mean ± SD was calculated for normally distributed numerical outcomes. Mean ± SD of demographic characteristics among PGC and OGC subjects was done using Mann Whitney test. Paired t test was used to compare non numerical variables between the two groups. Significance level was kept at P value ≤ 0.05 level.

Results

Of 672 patients diagnosed with COPD and DM in the study, 147 subjects were excluded, as they did not meet inclusion criteria. Also 14 patients in PGC and 21in OGC group were lost to follow-up. Finally 490 subjects of which 336(68.57%) had PGC and 154(31.4%) had OGC were analyzed (flow chart 1).

High proportion of patients in study group was males 346(70.6%) with 144(29.4%) females. Subjects with PGC had mean HbA1c of 9.92 ± 1.39 compared to 6.77 ± 0.65 of OGC group (p=0.0001). COPD patients with PGC had more severe disease compared OGC (Mean FEV1% predicted 48.47 ± 13.7 *vs* 67.4 ± 13.86, p= 0.0061) and also DOSE score (4.35 ± 1.88 *vs* 3.18 ± 2.30 p= 0.0052) at the baseline (Table-1). One of the important observations of the current study is that 119 out of 490 (24.29%) patients were newly diagnosed with DM following screening for the same. These patients were not aware of their diabetic status and 70.58% of these patients had poor glycemic control (Table-2).

After 1 year patients were re assessed to change in clinical condition from baseline to end of 12 months. Patients with PGC had statistically significant high rates of exacerbations as compared to OGC subjects (Table-3). When compared among the groups mean DOSE

Table 1: Baseline demographic characteristics of all participants.

DATA	PGC	OGC	P Value
Number of patients	336	154	
Male/female	243/93	103/51	
Age	67.46 ± 12.20	63.12 ± 10.64	0.164
BMI	18.28 ± 2.48	21 ± 2.32	0.216
Smoking (pack years)	7.14 ± 3.28	6.28 ± 3.19	0.085
Duration of COPD in yrs.	7.82 ± 2.3	6.83 ± 3.26	0.157
Duration of DM in yrs.	7.0 ± 4.84	7.42 ± 5.78	0.8112
Mean HbA1c	9.92 ± 1.39	6.77 ± 0.65	0.0001
Mean FEV1% predicted	48.47 ± 13.7	67.4 ± 13.86	0.0061
DOSE score	4.35 ± 1.88	3.18 ± 2.30	0.0052
MRC Dyspnea scale	2 ± 0.17	1.36 ± 0.79	0.0013
PAO_2 (mm of Hg)	63.77±7.85	76.92 ± 5.8	0.0016

score statistically greater in PGC patients after 12 months (Table-4) suggesting worsening of COPD symptoms, deteriorating health and quality of life. As far as duration of hospital stay is concerned PGC patients had significant longer duration of hospitalization (6.56 ± 1.70 *vs* 4.16 ± 1.26 p= 0.0004). About 8 patients of PGC and 4 of OGC group have died during the study period.

Discussion

Several studies have compared the severity and treatment outcomes of COPD patients with and without DM, but studies analyzing the impact of glycemic control among patients with co existing COPD and DM are very few. As per our knowledge, this is the first kind of study in India where outcome of COPD patients were compared in DM patients on the basis of glycemic control. Our study demonstrated that COPD patients with PGC had more severe COPD in the form of symptoms; higher dyspnea score, hypoxia, exacerbations and hospital stay compared to subjects with OGC.

COPD being a pro inflammatory state causes up-regulation of inflammatory cytokines by chronic inflammation and results in insulin resistance due to reactive oxygen species interfering with insulin receptor signaling. Exacerbations of COPD (AECOPD) cause acute stress response, which results in hyperglycemia. Other factors, which contribute, are obesity, sedentary lifestyle and smoking. Hypoxia is additional important entity which leads to impaired glucose tolerance and has reduced insulin sensitivity due to lipolysis. All these factors are likely to be exaggerated in DM patients leading to poorly controlled glycemic levels. In current study substantial number of patients had PGC (68.57%), which is significantly higher than general population. Also most of these patients had hypoxia with average PaO_2 of 63.77±7.85.

Table 2: Diabetic status among both the groups (known or new case).

Status of DM	Good controls	%	Poor controls	%	Total	%
Known case	119	77.27	252	75	371	75.71
New case	35	22.73	84	25	119	24.29
Total	154	100	336	100	490	100
Chi-square=0.0422 P = 0.8373						

Table 3: Comparing Exacerbation rate per year within the group (Baseline *vs* after 12 months).

Groups	Time	Mean	Std.Dv.	Mean Diff.	SD Diff.	Paired t	p-value
OGC	Baseline	0.36	0.66				
	12 months	0.59	0.8	0.23	0.81	-1.312	0.203
PGC	Baseline	0.63	0.76				
	12months	0.95	0.67	0.32	0.91	1.9014	0.043*

Previous studies have also established that COPD patients are more likely to develop insulin resistance. Hjalmarsen A et al revealed that COPD patients with chronic hypoxia have impaired glucose tolerance compared to COPD patients with normal arterial oxygen concentrations [15]. Bolton CE observed that in COPD patients, insulin resistance was increased compared to healthy matched controls and was related to plasma IL-6 and TNF a soluble receptor I concentrations [16]. The association between chronic inflammation and increased insulin resistance may be accounted for by disruption of insulin receptor signaling by inflammatory mediators [16]. Most of the COPD patients are treated with corticosteroids either in the form of oral therapy, systemic route or by inhalation. This is likely to affect the glycemic control significantly as one would expect. In a meta analysis of studies in patients with stable COPD, patients taking oral corticosteroids were 7.7 times more likely to have an adverse event than those on placebo, the most common of which were glucose intolerance and mild hypertension [18].

It is also important to note that hospitalization hyperglycemia is witnessed in significant number of COPD patients. AECOPD being an acute stressful event itself may lead to hyperglycemia and concurrent administration of systemic steroids make them more vulnerable to develop uncontrolled glycemic levels, which would be more worse in patients with DM. Baker EH, et al. observed that 50% of patients admitted to hospital with an acute exacerbation of COPD had random blood glucose >7mmol/L, although only 5% had a prior diagnosis of diabetes [19]. Of COPD patients requiring non-invasive ventilation for type II respiratory failure, 50% had random blood glucose >7 mmol/L and 7% had random blood glucose >11 mmol/L [20,21]. AECOPD are associated with increased systemic inflammation, which may exacerbate insulin resistance. AECOPD commonly cause type II respiratory failure with hypoxia and acidosis. In animals, respiratory acidosis caused glucose intolerance by inducing hepatic and peripheral insulin resistance [22]. Furthermore, AECOPD exacerbations are treated with oral or systemic corticosteroids, which increase the risk of hyperglycemia by 5 fold and lead to PGC [17]. Our study is in agreement with these observations as subjects with PGC had frequent and prolonged hospitalizations both before and after the registration in the trial.

Our observations of poor lung functions in COPD patients with PGC are in line with many previous studies. The Third National Health and Nutrition Examination Survey (NHANES III) [23] found that previously diagnosed DM patients had an FEV1 lower than that of non-diabetics. Impaired lung function was also greater in patients

Table 4: Mean DOSE score comparison within the groups.

Groups	Time	Mean	Std. Dv.	Mean Diff.	SD Diff.	% Of change	Paired t	p-value
OGC	Baseline	3.18	2.13					
	12 months	3.36	2.15	0.18	0.39	-5.71	-2.1602	0.0625
PGC	Baseline	4.35	1.88					
	12 months	4.77	2.21	0.42	0.96	-9.57	-2.9949	0.0044*

with poorly controlled diabetes, a finding that is not explained by their obesity or increasing age. Recently in 2013 Mahmoud M. El-Habashy, et al. [24] showed there was a significant decrease in pulmonary functions among DM patients (FEV1, FEV1/FVC%, PEF, FEF 25-75% and MVV) compared with healthy controls. Also in PGC subjects there was a remarkable reduction in FEV1, FEV1/FVC%, PEF, FEF 25-75% and MVV as compared with the OGC patients. To support this observation Ford, et al. showed that FEV1 and FVC values at baseline were inversely associated with the incidence of type 2 DM. Another important aspect worth revealing here is that this impaired pulmonary function is likely to deteriorate rapidly in uncontrolled diabetes [25]. This is in agreement with Fremantle Diabetes Study which showed that DM was associated with lower values of FEV1, VC, FVC and Peak Expiratory Flow (PEF) [26]. More importantly, they found that patients with DM had a greater rate of annual decline in pulmonary function and, in addition, that, DM related airflow limitation was associated with increased mortality.

DM is rapidly growing chronic non-communicable diseases in India. The long-term micro vascular and macro vascular complications of DM are responsible for mortality and morbidity. Poorly controlled DM further augments these complications. Many studies have demonstrated the benefits of OGC. United Kingdom Prospective Diabetes Study (UKPDS) study has shown that OGC control prevents death associated with diabetes-related complications [11]. The study concluded that a 1% reduction in mean HbA1c level was associated with a 12-43% reduction of microvascular and macrovascular complications. Despite of this, high proportions of DM patients remain poorly controlled in India. Difficulties to achieve OGC in our country are due to a limited access to the adequate health services, poor education level, lack of monitoring glucose levels, smoking, changing food habits, life style, urbanization and increasing elderly population etc [27].

COPD patients with PGC are challenge to the clinicians as there is escalating epidemic of these conditions in India. In the present study sizeable number of subjects (24.29%) was identified as DM patients first time after screening. This is an important observation as these patients were not aware of their DM status. Hence it is essential to screen all COPD patients for DM at the earliest. Achieving OGC in these patients should be the priority at all levels of health care services to avert negative impact of PGC on COPD patients. This would substantially reduce morbidity, mortality and cost of management of COPD and also improve the quality of life.

Strengths and Limitations of the Study

A major strength of our study is the prospective design, which avoided the problems of control selection in case control studies. Study focused on the specific group of patient's i.e. subjects with PGC and OGC in COPD. Availability of thorough DM details of all subjects made it possible to demonstrate a clear relationship between PGC and COPD treatment outcome. The detailed information on demographic, socioeconomic, and behavioral factors allowed us to eliminate major potential confounders as specific group at risk was targeted (subjects with PGC with COPD).

The study is limited by the fact that it is a single center study, results of which cannot be generalized. However, this provides a window of opportunity for clinicians and researchers to carry out further studies with involvement of different geographical areas across India. A large scale randomized controlled trial assessing the effect of PGC on COPD treatment outcome under a program setting would be worth exploring to answer many of unanswered issues in the field.

Conclusion

DM is a common comorbidity seen in patients with COPD. Majority of these patients have PGC, which severely affects the clinical course of COPD. Patients with PGC had more severe COPD, poor lung function, high symptom score, and increased risk of exacerbations with frequent and prolonged hospitalizations. Hence it is imperative to screen all COPD patients for DM. Achieving OGC in these patients should be the priority at all the levels of health care services to avert negative impact of PGC on COPD patients.

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