“EFFECT OF HYPERGLYCEMIA ON DURATION OF HOSPITAL STAY AND RATE OF MORTALITY IN PATIENTS ADMITTED WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE - A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY ”.

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LIST OF ABBREVIATIONS

COPD	Chronic Obstructive Pulmonary Disease
WHO	World Health Organisation
DM	Diabetes Mellitus
MS	Metabolic Syndrome
IDF	International Diabetes Federation
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
FEV1	Forced Expiratory Volume in one second
VC	Vital Capacity
ERS	European Respiratory Society
GOLD	Global Initiative for Chronic Obstructive Lung Disease
FVC	Forced Vital Capacity
DALY	Disability Adjusted Life Years
HbA1c	Glycated Haemoglobin
ADA	American Diabetes Association
BMI	Body Mass Index
HDL	High Density Lipoprotein
CVD	Cardiovascular Disease
NIDDM	Non-insulin Dependent Diabetes Mellitus
TG	Triglycerides
FFA	Free Fatty Acids
VLDL	Very Low Density Lipoprotein
Co A	Co-enzyme A

IRS	Insulin Receptor Substrate
MTOR	Mammalian Target of Rapamycin
ICS	Inhaled Corticosteroids
IL	Interleukin
NIV	Non-invasive ventilation
ICU	Intensive Care Unit
RR	Relative Risk
PEF	Peak Expiratory Flow Rate
FEF	Forced Expiratory Flow Rate
MVV	Maximum Voluntary Ventilation
MRSA	Methicillin Resistant Staphylococcus Aureus
FBS	Fasting Blood Sugar
RBS	Random Blood Sugar
PPBS	Post Prandial Sugar
AMA	Against Medical Advice

ABSTRACT

Introduction: COPD and DM, both being pro inflammatory conditions, they share relevant features in their genesis and course. COPD patients are more prone to develop type 2 DM due to multiple risk factors like obesity, sedentary lifestyle, smoking , oxidative stress and corticosteroid therapy. Prognosis of the COPD patients who are in exacerbation with hyperglycaemia are unknown. Thus this study has been taken up to analyse the outcomes of the COPD patients in exacerbation with diabetes mellitus.

Aim: To assess the effect of hyperglycaemia on duration of hospital stay and rate of mortality and other outcomes in patients of acute exacerbation of COPD.

Materials and Methods: The study was an observational study conducted for 1 year in a tertiary care hospital. 84 patients were enrolled and divided into two groups as group A and group B based on the mean random blood sugar levels. Group had 40 patients and group B had 44 patients. Outcomes of the COPD patients were compared between both the groups. Patients were further classified into controlled and poorly controlled groups with HbA1c cut off of 7.5 and compared with outcomes.

Results: Patients in the group B had poor outcomes compared to group A. The mean duration of hospital in group A was 5.43 ± 1.71 and in group B it was 7.34 ± 2.82 with overall mean duration was 6.43 ± 2.53 where p value was < 0.0001. The leading cause of exacerbation was infection which was up to 33.33%. The rate of mortality in group B was 11.36% and in group A it was 5.00% where p value was 0.2919. The mean duration of ICU stay was 3.33 ± 1.12 and 4.47 ± 1.60 in group A and B respectively with a p value of 0.0475 which is significant. In poorly controlled group,

mean number of exacerbation was 3.13 ± 1.24 which was higher than the group A which was statistically significant.

Conclusion: Hyperglycemia was associated with poorer outcomes in acute exacerbation of COPD patients. They had increased duration of hospital stay and rate of mortality. Hence optimal glycaemic control and screening of all COPD patients for diabetes mellitus is mandatory to improve the outcomes.

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INTRODUCTION

COPD represents a significant public health challenge and is a major cause of hospital admissions all over the world. It is the third most principal cause of mortality all over the world currently.[1] The load of this disease is estimated to raise in the future because of persistent exposure to causative factors and population ageing.[2] Severe exacerbations of COPD are associated with a significantly poorer survival outcome. The precautionary measures for COPD should be taken more because of its effect on other systems especially cardiovascular system and other comorbidities[3].

According to WHO estimates, 65 million people have moderate to severe COPD. More than 30 lakhs of population died of it in 2012, which corresponds to 6% of all deaths throughout the world. Approximately 85% of deaths of COPD occur in developing countries[4].

In 2018, the COPD prevalence in India was 4·2%. India has got more prevalence of COPD than the global average. COPD is ranking as the 2nd common cause of disease burden in India. The crude prevalence of COPD in India increased by 29% from 1990 to 2016. This increased rate of burden from COPD is due to concerns associated to its fairly late identification and management, even with the developments in health facility over time in India.

Smoking tobacco is the significant risk factor. However, as noted above, never smokers also develop COPD and women outweigh men in this cohort.[5] Indoor and outdoor air pollution are probably the next predominant risk factor associated with COPD. Other factors comprise second hand exposure of tobacco, age, duration of exposure in polluted areas, a COPD family history, tuberculosis, hospital admission for any respiratory illness in the childhood.

COPD is often a contributory factor to the cause of death. It is likely therefore that the use of death rates from certification of these conditions underestimates the true mortality due to COPD. Most of the mortality from this condition occurs in the age group of 65 to 70 years. Comorbid conditions may worsen the outcomes of COPD patients and may have an effect on the patient's health condition and treatment of COPD. A newer study had projected that COPD would be the fourth principal cause of mortality by 2030.[6]

Around 450 million people are suffering from diabetes mellitus in the world. In an adult population, the age-identical prevalence of diabetes in the world has nearly doubled in the past 40 years, rising from 4.7 to 8.5%.The biggest raise in the prevalence of diabetes mellitus is reported in underdeveloped and developing countries.[7] India has the 2nd highest number of people with impaired glucose tolerance and poorly controlled diabetes mellitus accounting up to 69.4 million people worldwide.The most common type is type II diabetes mellitus.

COPD and DM share relevant features in their genesis and course due to their inflammatory pathology. COPD patients are predisposed to develop impaired glucose tolerance due to several risk factors like obesity, sedentary lifestyle, smoking , oxidative stress and corticosteroid therapy. COPD, when associated with DM has a 26 to 27% elevated risk of mortality. Poor glycemic control is associated with alteration in lung volumes and reduction in FEV1, diffusion and vital capacity which can be due to diabetes associated microangiopathy[8]. Management of diabetic patients and treating them with insulin will improve the reduction in gas transfer.[9]

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.[10] Decrements in the pulmonary function of diabetic population are thought to be the consequences of altered biochemical reactions in the connective tissue elements such as collagen, as well as damaging of the blood vessels due to the glycosylation of proteins and amino acids induced by persistent hyperglycemia.[11]

Patients with both COPD and diabetes mellitus have elevated issues of infection and sepsis with predominantly gram negative organisms growing from blood and sputum culture during acute exacerbation. They require higher antibiotics compared to those without diabetes. Several studies have observed that hyperglycaemia can increase the worsening of the outcomes and prognosis of COPD patients, increasing the odds of COPD-related mortality . On the other hand, diabetes-associated adipose tissue storage has been observed to have a defensive effect in patients with COPD, even reducing mortality. Controversy remains as to whether there is a causal relationship between T2DM and COPD, and it is also possible that this interaction only occurs in a subset of patients.[12]

Both COPD and DM poses a huge challenge to the physician owing to its growing incidence in India and western countries. Many studies done in countries outside India has signified the poor outcome of COPD patients with co existing DM compared to those without DM. Only few studies in India has been done linking hyperglycemia and acute exacerbation of COPD and it has not been clearly understood that how poor glycemic control is detrimental for COPD patients and their outcomes. So this research work has been taken up to assess the effect of hyperglycemia on the outcomes of acute exacerbation of COPD patients.

OBJECTIVES

1. Primary objective

To evaluate the effect of hyperglycaemia on duration of hospital stay and rate of mortality in acute exacerbation of COPD patients.

2. Secondary objective

To assess the effect of hyperglycemia on other outcomes including duration ofICU stay, duration of treatment with non-invasive ventilation, requirement of invasive mechanical ventilation, duration oftreatmentwith intravenous corticosteroids and requirement of more than 1 antibiotic in patients with acute exacerbation of COPD.

REVIEW OF LITERATURE

1. Definition of COPD

GOLD 2018 (Global Initiative for Chronic Obstructive Lung Disease 2018) defined COPD as " a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."

The chronic airflow limitation is a combination of parenchymal destruction and small airways disease which can vary from person to person. There is an association among the duration of smoking and the severity of the airflow restriction, but there will be massive individual variation.[13] Smoking population have a decline in FEV1 of 60 - 70 ml/yr approximately, even though only a proportionate amount of smoking population has COPD changes.

The chronic inflammation caused by small airway disease evokes structural changes and narrowing of the small airways. The destruction of the lung parenchyma by inflammatory processes, oxidative stress, or protease/ant protease imbalance decreases the number of alveolar attachments on the small airways, decreases lung elastic recoil, and limits airflow. The inflammation extends beyond the lungs to produce systemic consequences. Hence this disease is a complex, heterogenous disease, multicomponent with several complications, the clinical and radiological presentation of which varies in individual even with similar severity of airflow limitation.[14]

COPD is a heterogenous condition with pathologic changes in the large and small airways (chronic bronchitis and bronchiolitis) and lung parenchyma (emphysema) that vary greatly in their expression among the patients.[15] Chronic bronchitis is defined as the presence of sputum and cough production for most of the days of 3 months for 2 consecutive years. Emphysema is defined as dilatation of the airspaces distal to the terminal bronchioles, due to alveolar wall destruction.

A major site of airflow restriction is the small conducting airways (<2 mm in diameter).[16] Niewoehner and colleagues observed that inflammation consisting of neutrophils and macrophages could be visualized among the smaller airways of smoking patients who were expired due to other diseases in the hospital.[17] Several researches have observed that pathogenesis occurred in small airways of smokers with COPD and also even without COPD changes.[18] There exists a correlation between the disease severity and the percentage of obstruction of the airway lumen by inflammatory exudates.[19]

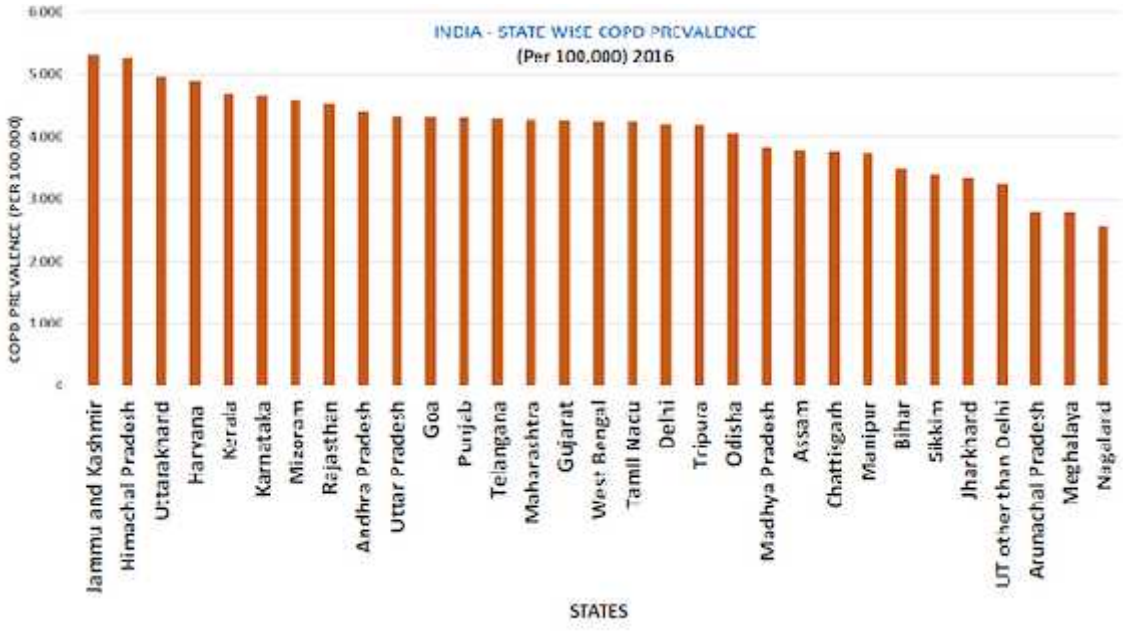
2. Epidemiology of COPD

The Global Burden of Disease reports a prevalence of 251 million COPD cases in 2016 globally. Globally, it is calculated that 3.17 million deaths were caused by the disease in 2015. More than 85% of deaths in COPD occur in underdeveloped and developing countries. Two significant issues to contemplate when addressing the burden of COPD all over the world are that of reduced identification of the disease and associated comorbidities. COPD is not at all investigated and diagnosed in many jurisdictions. Studies concentrating on the worldwide financial burden of COPD are all based on previously diagnosed and treated COPD and multiplication of these

estimates by the number of patients with COPD to compute the financial burden of COPD will undervalue the input of patients with COPD who are underdiagnosed.[20]

The BOLD (Burden Of Obstructive Lung Disease) study found a global prevalence of 10.1%. Men were found to have a pooled prevalence of 11.8% and women 8.5%. The numbers vary in different regions of the world. Among the countries all over the world, South Africa has the highest occurrence affecting 22.30% of men and 16.80% of women meanwhile Germany has the lowest prevalence of 8.62% for men and women.

Figure 1. COPD prevalence in India - statewise



The WHO has estimated that mortality rates due to COPD will increase by around 160% in the Southeast Asian region over the next two decades. Half a million people are estimated to die due to COPD in India every year, the second largest number in the world after China. Murthy and his colleagues have shown that it may average around 5 – 6 % in the adult population with higher rates in smokers, male sex,

rural areas, depending on the type of domestic fuel use and socioeconomic status.[21] A multicentric study involving 35296 subjects performed in 2006 showed that COPD is 2.66 times common in smokers compared to non smokers. The study showed prevalence of around 5.1% in males and 3.2% in females.

Crude evaluations specify that there are approximately 30 million patients of COPD in India. Prevalence of COPD in India ranges from 2.13% to 9.34 % in male population and it ranges from 1.37 % to 1.50 % in female population.Malik et al reported that chronic bronchitis has an occurence of 9.3% in rural and 3.7% in urban male population and 4.8% in rural and 1.5% in urban female population.

A study conducted by Rayetet al.[23] in south India revealed a prevalence of 4.08% in males and 2.55% in females with male to female ratio having 1.6. The Population ageing is about to become the next community health challenge. The older persons number in the population is increasing by 2% every year. It contributes to the alarming increase in the overall tally of COPD in the current population.

Morbidity of COPD

COPD contributes to significant morbidity which is associated with the worsening of the quality of life; 80% of patients hospitalized following an exacerbation state a health status rated by a physician as being worse than death. The patients who survive their first COPD-related hospitalization, up to 50% are reported to be readmitted within six months of discharge. Several research works had observed that morbidity raises with age and it prevails greater in men than in women. It can also be exaggerated by diseases like diabetes mellitus, hypertension and other

cardiovascular disorders that may interfere with treatment of COPD or may have an effect on health status of the patient.[24]

Mortality of COPD

COPD was considered as the 6th most significant disease responsible for mortality in 1990 worldwide; however, with increased cigarette smoking, especially in developing nations, it is projected that COPD will be the 3rd foremost causative factor of mortality in the coming years.Globally, it is calculated that 3.17 million deaths were caused by the disease in 2015. Total deaths from COPD are projected to increase by more than 30% in the next 10 years.

According to University of Washington's study in 2018, COPD was the second highest contributor of death in India after heart disease in 2017, killing 1 million (958,000) Indians in that year. The rate of mortality is upto 111 per 100,000 population which was more in males than females. It is probably due to the increased epidemic of smoking and people living longer than usual.

Financial burden of COPD

COPD contributes a huge economic loss, not only for the patient but also for the nation. The burden is estimated as 38.8 billion US$ for US and 38.6 billion US$ for Europe. The evaluated financial burden due to COPD for India is 30,000 crores. Up to 82% of the costs involved in COPD are due to inpatient hospitalizations. Loss of productivity due to COPD accounts for between 40% and 67% of the overall costs across the world. COPD is, therefore, a major financial burden for countries throughout the world. India spent an estimated 25,210crores for COPD in the year

2006. A large part of this expenditure is because of delayed diagnosis and improper management.

A study done in Karnataka in southern India had the total direct expenditure of treatment up to Rs. 29,887 ± 11,997 and the total mean indirect treatment expenditure accounted up to Rs. 28,135 ± 2,225. The mean value of the absenteeism caused due to COPD from the job was approximately 193 ± 32 hours for a month. Therefore, a systematic protocol for treatment and management strategies will help in reducing the morbidity, mortality and financial burden.

3. Risk factors

a. Genetics

Obstruction of airflow has been observed in siblings of patients who are smoking,[25] which suggests that environmental factors and genetic causes could impact the susceptibility. Alpha 1 antitrypsin deficiency, an inhibitor is considered as the significant genetic causative factor for emphysema development. Other genes have minimal risk for contribution of development of airflow obstruction and development of COPD such as the hedgehog interacting protein gene, the FAM 13 gene and the MMP12 encoding gene.[26]

b. Smoking

CigaretteSmoking is the most frequently encountered risk factor for COPD. Smokers have an elevated severity of respiratory symptoms, decreased FEV1, loss of lung density, and an elevated mortality rate when compared with nonsmokers.[27] The important factor was found to be the smoked quantity and the amount inhaled. There was no significant difference found between cigarettes with and without filters in

altering pulmonary function. Tobacco and marijuana were also considered as one of the principal causative factors for COPD.[28] Cessation of smoking has been correlated with both reduced occurence of COPD symptoms and a decline in reduction of FEV1 in patient cohorts.[29]

c. Air pollution

Several studies have commented that greater levels of outdoor and indoor pollution of air were significantly correlated with cough production, breathing difficulties and reduced ventilatory function. Exposure to particulate and nitrogen dioxide has been correlated among impaired ventilatory function in adults and reduced growth of lung in children. Exposure to biomass fuels in homes with poor air circulation has been reported to be an important cause of COPD among women in developing countries.[30] Exposure to sulphur dioxide is also corelated with chronic bronchitis. The WHO estimated that more than 10 lakhs of population die in an year due to COPD exaggerated by air pollutants.[31] International advocacy organizations such as the Global Alliance for Clean Cook-stoves seek to curb indoor air pollution.

d. Asthma and hyperreactivity

Asthma is also considered as an important causative factor for emphysema development. A Dutch research found that 20% of the patients with asthma had irreversible airflow limitation.[32] A Danish observational study mentioned that bronchial asthma was associated with a huge decline of FEV1[33]. Hyperreactivity of the bronchus had been considered as the second foremost causative element for COPD which is accountable for 16% of the risk which is attributable.[34] This statement is in agreement with above mentioned studies suggesting a huge effect of

hyperreactivity of bronchus on reduction in FEV1 even without the proof of bronchial asthma.

e. Infection

Increased lower respiratory tract infection in childhood has been correlated with decreased pulmonary function and a significant decline in FEV1 in adulthood.[35] In cases of established COPD, great importance has recently been given to recurrent infections and exacerbations secondary to infections. Recurrent infections have a significant role in pathogenesis of COPD. The most common cause of exacerbation is infection and these exacerbations increase further reduction of FEV1, eventhough the original effect is not up to it.[36]

f. Occupational exposure

Exposures seen in occupation are considered as a principal causative factor for COPD.[37] NHANES III survey observed that the part of COPD accountable to exposures secondary to occupation had an overall value of 19%. It had observed up to 31% among nonsmokers.[38] These results correlate with a statement given by American Thoracic Society. It showed that the work related consequences sum up to 20% of clinical features and derangement of the function of lung consistent with COPD**.**

g. Socioeconomic status

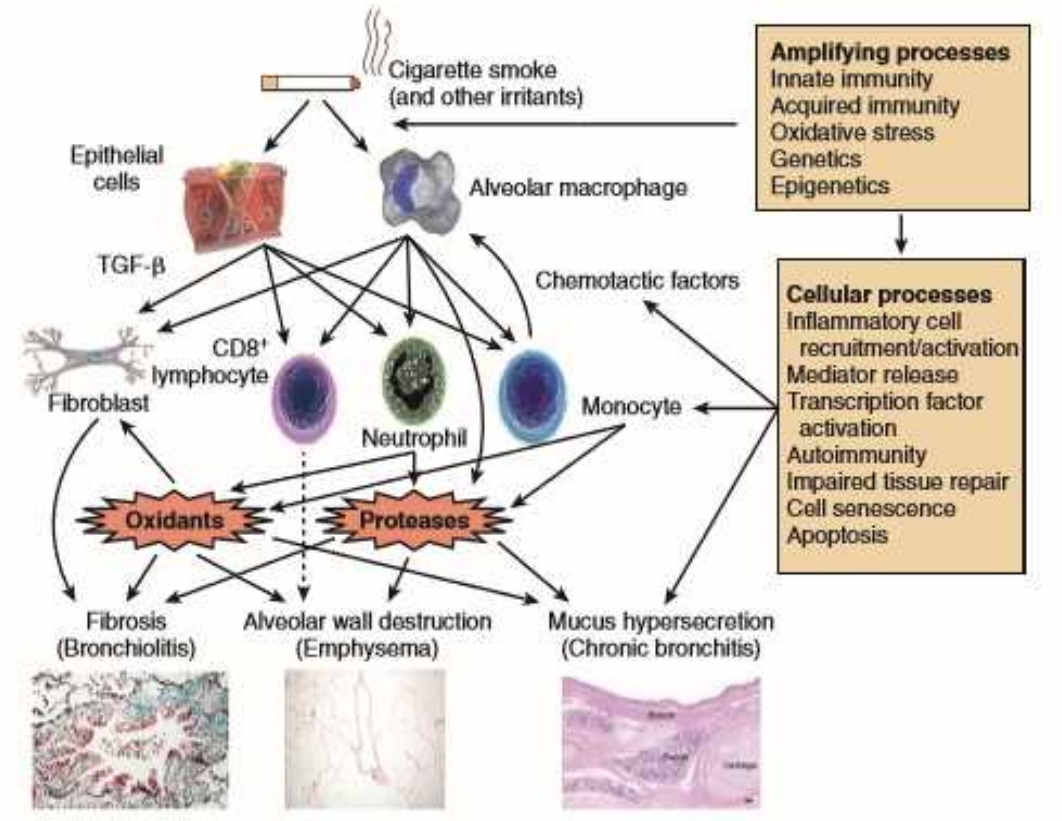
Poor socioeconomic status is a principal causative factor correlated with COPD. It is associated with improper spacing in the house, poor nutrition, recurrent upper and lower respiratory tract infections among the children, exposure to cigarette

smoke, work related exposures, smoke from the biomass and indoor pollutants. These factors increase the risk of COPD. Thus, socioeconomic class must be treated as a significant causative factor for progression of pathogenesis of COPD.[39]

4. Pathogenesis of COPD

As mentioned in the COPD definition, inflammation plays a principal role in present concept about its pathophysiology. The inflammation pathway is that inhaled irritants enrolment of neutrophils, macrophages and other inflammatory cells and the end products of these enrolled cells cause derangement of alveoli and lung parenchyma and modify the pathogenesis of parenchyma. Cell mediated and humoral immunity were involved in pathogenesis of emphysema leading to irreversible changes.

Figure 2. Overview of pathogenesis of COPD



CD4+ lymphocytes, CD8+ lymphocytes and B cells gather in alveolar and small airways and form BALT in the bronchial walls.[40]The increasing BALT presence in airways proportionate with COPD and its severity.

In the epithelium and submucosa of the bronchus in COPD patients, monocytes are the principal cells with scattered neutrophils.[41] T lymphocytes predominate in the monocyte constituent especially CD8+ cells and macrophages. The ratio of CD8+/CD4+ increases in COPD.[42] There is a 10 fold raise in the monocytes and macrophages number in the parenchyma of lung and in patients with COPD. Category of the airflow limitation in COPD patients correlate with the quantification of macrophages in the small airways. Smoking cigarette induces production of inflammatory cytokines such TNF-α, IL-8, and other CXC chemokines through macrophages.[43]

a. Cytokines and chemokines

In patients with advanced lung disease, lymphocytes present in the airways boldly release TH1 cells and produce interferon (IFN)-γ and CXCR3. This accumulation of lymphocytes dominates in increased severity. The accumulation will be towards the cells with phenotype of TH1. TNF-α has also been caught up in cigarette smoke induced pathogenesis of COPD. Animals that secretes more TNF-α show emphysematous changes and an increased response of alveolar inflammation. TNF-α receptor absence was correlated with decreased responses of inflammation in the alveoli. Development of emphysema is also contributed by the increase in the levels of IL-1β.

b. Airway remodelling and limitation

The peripheral airways are the principal site of increased resistance to airflow in COPD. The main pathogenesis in the peripheral airways comprise elevated number of inflammatory cells and important anatomical changes, such as metaplasia of the goblet cell present in the epithelium, fibrosis of the airway wall and hypertrophic changes in the smooth muscle.[44] The increase in the airway lumen thickness, inflammation and hypertrophic changes will reduce airway diameter.

c. Protease/antiprotease imbalance

Increase in the levels of proteases or decreased production of antiproteases ends in imbalance. This fact is developed from the reports where they showed the progression of early-onset emphysema especially anti-elastase α1-antitrypsin (A1AT) deficient patients.[45] Cigarette smoke aggravates oxidative stress leading to promotion of raised inflammatory cells to secrete a mixture of proteases and inactivates most of the antiproteases. The principal proteases involved are the matrix metalloproteases (MMPs) and cysteine proteases. The principal antiproteases concerned in the pathophysiology of COPD include inhibitors of MMP and alpha 1 antitrypsin.

d. Oxidative stress

Cigarette smoking which is a significant source of oxidants lead to accumulation of reactive oxygen species which are produced by inflammatory cells.There is a disproportion between oxidants and antioxidants leading to increased production of reactive oxygen species, which is one of the important pathogenic mechanisms in COPD.[46] Most of the inflammatory markers suggestive of oxidative stress are elevated in COPD patients who are stable and are elevated during

exacerbations. Oxidative stress leads to inactivation of antiproteases and accumulation of mucous and secretions. It will also aggravate inflammation by promoting several pathways such as nuclearfactor-κB which enhances activation of kinase and genetic factors which will cause increased synthesis of proinflammatory mediators.

e. Mucous hypersecretion

Several stimulating factors like lipopolysaccharides (LPSs), TNF-α, IL-1β and oxidative stress cause goblet cell metaplasia and mucus hypersecretion.[47] Cigarette smoke produces reactive oxygen species, which results in activation of vascular endothelial growth factor receptor (VEGFR) and increased mucus secretion by promoting TNFα converting enzyme leading to the loss of TGF-α in bronchial epithelial cells.[48] Smokers show raised levels of FGF in the airways, mostly because of increased levels in the glands present in the bronchus. This indicates that FGF play a significant role in inducing mucus secretion and bronchoconstriction in smokers.[49]

f. Airflow limitation and gas trapping

The degree of fibrosis is associated with the decrease in FEV1 and ratio of FEV1/FVC. This is correlated with accelerated decline in condition of the COPD patients. Airflow limitation in peripheral small airways trap gas at the time of expiration which may lead to hyperinflation. Inspiratory capacity is reduced by static hyperinflation and corelates with dynamic hyperinflation which may lead to dyspnoea and derangement of exercise capacity. They cause derangement of intrinsic functions of respiratory muscles. It is believed that emphysematous changes develop very early in COPD and may be responsible for exertional dyspnoea. Bronchodilators act on

dilating small airways reducing bronchoconstriction, air trapping leading to reduction of lung volumes and improvement in exercise capacity.

g. Gas exchange abnormalities

Gas exchange abnormalities lead to hypoxemia and CO2 retention and has various pathogenesis in COPD. Gas transfer reduces while the disease becomes severe. Reduced ventilation may also be due to more dead space ventilation or decreased drive for ventilation. This may cause hypercapnia and narcosis especially when it is associated with decreased ventilation and its drive, due to raised efforts to breathe because of dynamic hyperinflation added with severe limitation and respiratory muscle impairment. Reduced ventilation in the alveoli and a decreased vascular bed adds the worsening leading to abnormalities of V/Q ratio.

Inflammatory response in blood vessels is also seen in emphysematous lungs with endothelial cell abnormality. The increased damage to the pulmonary capillary bed in COPD may lead to increase in the number of pulmonary capillaries. This may lead to pulmonary artery hypertension leading to right ventricular failure. Pulmonary artery diameter as noted on CT scans was in association with risk of exacerbation irrespective of the previous number of exacerbations. Even in mild cases, significant changes in pulmonary capillary blood flow occurs which may worsen the disease leading to increased risk of exacerbations and thereby increasing the risk of infections, morbidity and mortality.

5. Classification of COPD severity

According to the GOLD criteria 2018 for diagnosing COPD, post bronchodilator value of FEV1/FVC ratio < 0.7 is considered. The severity of airflow limitation is

classified based on the post bronchodilator FEV1. The classification of airflow limitation is as follows.

Figure 3. Classification of airflow limitation severity in COPD

In patients with FEV1/FVC < 0.70		
GOLD 1	Mild	FEV1 ≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3	Severe	30% ≤ FEV1 < 50% predicted
GOLD 4	Very severe	FEV1 < 30% predicted

6. COPD and its co-morbidities

In COPD co-morbidities may be defined as chronic medical conditions that affect persons who have COPD. They differ from systemic complications associated with COPD. However both the diseases influence the course.[50]They may have similar pathogenesis with COPD. They have an effect on health status, utilisation of the facilities of healthcare and all-cause admissions and mortality in COPD patients. Mortality due to the comorbidities may occur prior to respiratory causes.

Classification of co-morbidities of COPD

1. Respiratory system: Bronchial asthma, pulmonary thromboembolism, pulmonary artery hypertension, obstructive sleep apnoea and lung malignancy

2. Cardiovascular system: Ischaemic heart disease, arrhythmias, congestive heart failure, heart block and hypertension

3. Metabolic: Metabolic syndrome, diabetes mellitus, osteoporosis, hypertension and dyslipidaemia.

4. Malignancy: Lung carcinoma, bone tumour and gastric carcinoma

5. Psychiatric: Bipolar disorder, anxiety disorder and insomnia

6. Miscellaneous: Renal failure, chronic liver disease, acid peptic disease and pancreatitis.

The foremost important cause of death in patients with COPD is due to cardiovascular diseases. In a study done by MANNINO et al., the diseases affecting cardiovascular system (defined as ischaemic heart disease, heart failure, stroke and/or transient ischaemic attack) was present in around 22% of COPD patients compared with 9% in patients without COPD.[51]

COPD and metabolic syndrome

Metabolic syndrome is one of the complex disorders observed with features of increased central obesity, raised triglycerides, atherogenic complications associated with fat metabolism, raised blood pressure and impaired glucose tolerance and altered insulin sensitivity. COPD patients usually have any of the constituents of the metabolic syndrome and osteoporosis.[52] Hypertension is considered as one of the foremost comorbid diagnoses in COPD. Mannino et al.[59] conducted a epidemiological population based cohort study and stated that the hypertension prevalence was 32% in normal population, which elevated in COPD patients based on the severity. 40% prevalence in GOLD stage I patients, 44% in GOLD stage II and 51% in GOLD stage III and IV patients.

Diabetes mellitus is commonly found in moderate to severe COPD patients than in the normal population. The prevalence value is 12.7% overall.[53] Although some of the normal COPD patients will be having hyperglycaemia aggravated due to corticosteroids, most of the patients must be having overt diabetes.

Studies on altered lipid metabolism in patients of COPD are not available in vast and have relied on questionnaires toanalyse frequency; the prevalence based on these studies is between 9% and 51%. The most common cause of drug-related osteoporosis is systemic corticosteroids. A cross sectional study mentioned that up to 45% of subjects with COPD who were eligible for rehabilitation had significant muscle wasting.[54]

Diabetes mellitus

Diabetes mellitus is one of the foremost health problems facing mankind and is a major public health problem. According to the recent data, an assessed 462 million people have impaired glucose tolerance and diabetes mellitus all over the world. The number is projected to almost double by 2030. Although India has now been bettered in the top spot by China, until now she had much more diabetic population compared to any other country world wide[55].More than 63 million populations in India are affected by diabetes mellitus, which equals to around 7.3% of the general adult population. The mortality rate of diabetic patients in India is high. Around 1 million people in India die because of diabetes in each year. The common category of diabetes is type 2 diabetes mellitus. The prevalence is 2.7% in rural areas and 11.8% urban areas for type 2 diabetes mellitus. Impaired glucose tolerance prevalence is high in the urban areas. Impaired glucose tolerance is common for the people under 40 years of age than diabetes mellitus

According to a recent data, India is considered to comprise around 109 million people with impaired glucose tolerance and diabetes mellitus by 2035.[56]A study by the ADA states that India will have much more increase in diabetic patients by the end of 2030. This incidence is accredited to various reasons including genetic causes, high intake of calories, reduced physical activity and sedative lifestyle by India's growing young and middle income population.

Type 1 and 2 diabetes are the most common types of primary diabetes mellitus. This classification is necessary in evaluating the requirement of treatment and also in realizing the causes of hyperglycaemia which are completely different in pathogenic mechanisms.

1. **Type 1 Diabetes Mellitus**

Type 1 diabetes mellitus occurs due to the β-cells destruction in the islets of pancreas with resulting loss of insulin production. A combination of environmental and genetic factors that trigger an autoimmune response on the β-cells is responsible, occurring in genetically susceptible individuals. Thus, in type 1 diabetes, monozygotic twins who are identical has concordance of one-third of the pairs where as in type 2 diabetes almost all pairs are concordant. The steps of destruction of islet cells begins in childhood and is known to start several years before the clinical onset of diabetes.

2. **Type 2 Diabetes Mellitus**

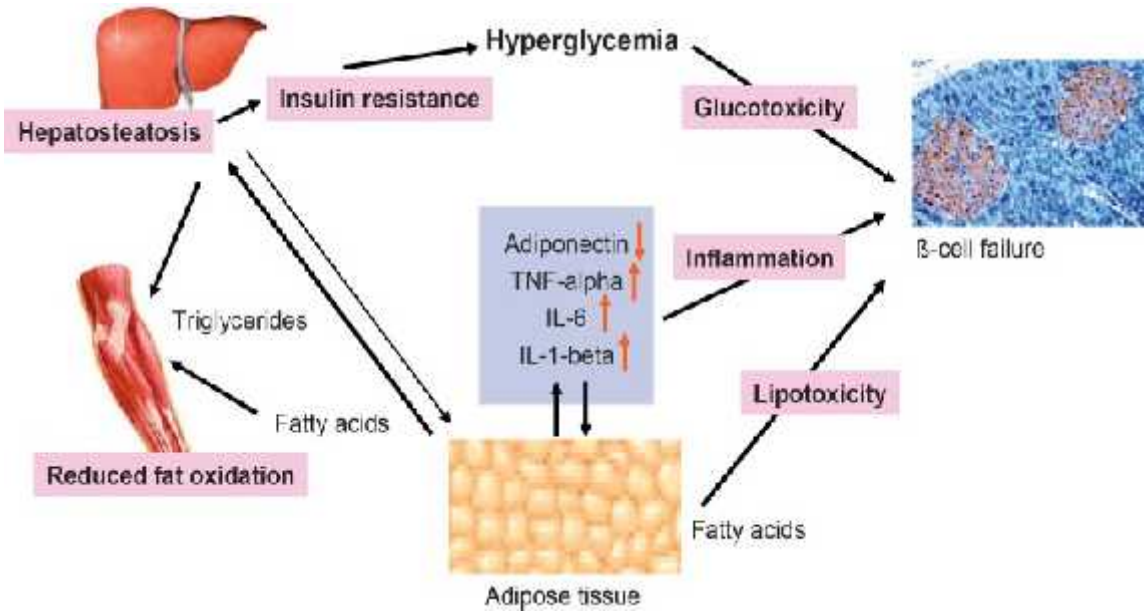
This is the most common form of diabetes all over the world, accounting up to 90% of all the cases of diabetes in total. There are various causes associated with type 2 diabetes, which include a wide range of diseases with varying onset and

progression. The pathogenesis is either because of the reduced secretion of insulin due to islet cells destruction associated with raised peripheral resistance in the skeletal muscles to the action of insulin resulting in impairment of glucose tolerance, or increased gluconeogenesis. Most of the type 2 diabetic patients which is around 97% of them have cause as idiopathic where there is no specific causative defect.

Pathogenesis of diabetes mellitus

Thepathogenesis of diabetes involves combination of insulin resistance peripherally and failure of pancreatic beta cells progressively. According to a scenario, resistance of insulin occurs when adipose cells reach an adequate size and storage of adipose tissue becomes limited. Fatty acids and triglycerides present ectopically starts promoting insulin resistance in liver and skeletal muscle. In addition to it, inflammatory state worsens which is present for a long time, caused due to infiltration by immune cells into the adipose tissue, promotes insulin resistance. Fatty acids also appear to trouble function of β cells leading to lipotoxicity, mostly in association with the exposure of cells to raised glucose levels leading to glucotoxicity. This mechanism occurs when a polygenic susceptibility reacts with exogenous causes like smoking, poor nutrition, central obesity and reduced physical activity. Thus, diabetes mellitus is a complex entity affecting multiorgans which has a genetic origin and pathology but is aggravated by other exogenous factors.

Figure 4. Pathogenesis of Diabetes mellitus



Mechanism of β-Cell Failure

Several studies have indicated that large levels of accumulation of fatty acids and lipids is a causal factor in the initiation of diabetes. In addition to it, it has been proven that incorporation of large number of fatty acids in pancreatic islets can promote apoptosis of β-cells. When fatty acids accumulate in non-adipose tissues during increased levels of nutrition, fatty acids cause the formation of ceramide. It is a toxic substance composed of lipids and mostly the cause of lipoapoptosis. It has also been emulated that raise in post-prandial and absorptive blood sugar levels could be the cause of glucotoxicity (damage of pancreatic beta cells). According to this concept, the β-cell of pancreas is highly prone for oxidative degradation or is sensitized by a low anti-oxidative content. It was formulated that raised blood sugar levels lead to increased levels of reactive oxygen species which may further lead to loss of essential transcription factors such as Maf A, and an irreversible cell damage.

Insulin resistance

The term insulin resistance indicates the presence of deranged response to either endogenous or exogenous insulin. Resistance of insulin is primarily established by reduced insulin induced transport of glucose, altered metabolism in adipocytes and skeletal muscle, impaired insulin suppression of adipocyte lipolysis and hepatic glucose output. However, it came to a conclusion that individuals with altered insulin sensitivity have disorders of multiple metabolic pathways involving amino acids, glucose and lipid metabolism.

Various factors like age, ethnicity, central obesity, physical activity and medications influence insulin sensitivity. Substantial data indicate that insulin resistance plays a vital role in the initiation of IGT and diabetes.

Obesity and insulin resistance

The correlation of obesity with T2DM has been recognized for years. A close relationship among altered insulin response and central obesity is seen in all kinds of population and is observed among all ages and various ranges of body weights, across all ages, and in both sexes. Several epidemiologic studies have observed that the risk of diabetes and resistance of insulin raises as fatty adipose tissues increase which implies that the absolute fat content of the human body has an effect on altered sensitivity of insulin across a broad range.

Central (intra-abdominal) adiposity is more strongly linked to insulin resistance than total adiposity and is also further associated to a number of significant factors like increased plasma glucose, cholesterol, insulin, increased triglyceride levels and reduced high-density lipoprotein levels.

The reason for the relationship between intra-abdominal fat and abnormal metabolism is not adequately understood, but a number of hypotheses has been proposed. First, abdominal fat is more lipolytically active than subcutaneous fat, perhaps because of its greater complement of adrenergic receptors. In addition, the abdominal adipose store is resistant to the antilipolytic effects of insulin. This might change adipocytes to increase lipolysis and alter the production of adipokines, which may directly modulate glucose metabolism.

Criteria for diagnosis of DM

Tolerance levels of glucose is divided into three main categories namely normal glucose homeostasis, impaired glucose homeostasis or diabetes mellitus. The exact diagnosis of these categories rests on the measurement of glycemia. Criteria for the diagnosis of diabetes mellitus is shown in the table below. The American Diabetes Association criteria for diagnosing diabetes mellitus is mentioned below.

Figure 5. ADA Criteria for the diagnosis of diabetes mellitus

- Symptoms of diabetes plus random blood glucose concentration ≥ 11.1mmol/L (200mg/dl) or
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dl) or
- HbA1c ≥ 6.5%
- 2 hour plasma glucose ≥ 11.1 mmol/L (200mg/dl) during an oral glucose tolerance test

Most commonly fasting plasma glucose or the glycatedhaemoglobin is used as a screening tool for assessing diabetes mellitus is recommended because

(1) Most individuals who meet this recent criteria for diabetes mellitus are asymptomatic and not screened. Finally they remain unaware of this disease.

(2) Population based studies state that type 2 diabetes mellitus may be present for greater than 10 even before the diagnosis.

(3) Some of the diabetic patients usually have one or the other complications of diabetes during the time of presentation.

(4) Screening for type 2 diabetes mellitus and its management may favourably alter the natural history of DM.

COPD and the risk of Diabetes Mellitus

Diabetes mellitus is a common comorbid condition associated with COPD.[57] Most of the studies have observed that diabetes mellitus is frequently correlated with reduced lung function. The complications comprise several pathological mechanisms and those mechanisms which involve lung as a target organ for microangiopathy secondary to diabetes mellitus.

Metabolic syndrome almost affects 22–54% of COPD patients and in several studies, it was shown to be more common in earlier stages of COPD. Diabetes mellitus involves up to 37% of patients with COPD, depending on the patient subgroup studied. Metabolic syndrome is 1.3–1.5-times more common in COPD patients than in people with normal lung function. According to Cazzolaet al.[58] the prevalence of DM in COPD is 18.8%. According to Manninoet al.[59] the prevalence is 13.6% in an all-stage COPD population.

Incalazi et al.[60] stated that from a group of 250 COPD patients who were admitted for exacerbation, the second most common comorbidity was diabetes mellitus. The median survival was 3.1 years and 228 out of 270 patients died during

the follow up period. The prevalence of metabolic syndrome is 22.5% for all grades according to Ghanassiaet al.[61]

A study conducted in Japan stated that the patients with diabetes mellitus but with controlled blood glucose levels during exacerbation of obstructive lung disease also has impact on long term mortality. Out of 153 patients, 57 of them expired during the observational period and impaired glucose tolerance was strongly associated with elevated mortality.

A retrospective analysis examined the relationship among the comorbid conditions and COPD using Health Search database information obtained from Italian College of General Practitioners that says information of around > 1 % of the population. Compared to the non COPD individuals, COPD patients were at higher risk of developing impaired glucose intolerance, 10.6 % in the normal adult population vs. 18.8 % in COPD patients.[62]The Framingham Heart Study has reported that significant relationship exists between glycemic control and impaired lung function.[63]

In the Fremantle Diabetes Study in Australia, 125 diabetic patients without lung abnormality and respiratory complaints were assessed with pulmonary function test at baseline and after 7 years. The study stated that the decline in FEV1 was 72 ml/year compared to an expected decline of 25–30 ml/year in healthy non smokers, stating that the exposure to blood glucose may be a strong and consistent negative predictor of pulmonary function follow-up.[64]

Lazarus et al.[65] reported that reduced FVC was correlated with the risk of having higher levels of insulin resistance and similar correlations have been found for

maximal mid-expiratory flow rate (MMEF), stating that the insulin resistance could be the factor correlated with the derangement of pulmonary function.

Song et al.[66] observed results of the health study in which > 38,000 women were without diabetes mellitus. All the subjects were followed up to 12.2 years. Women who were diagnosed with COPD had a multivariate relative risk of 1.38 for diabetes mellitus.

Heianzaet al.[67] analysed 5,346 male subjects without diabetes or COPD to analyze the effect of reduced pulmonary function on the incidence of diabetes mellitus. They proved that decline in FEV1 and FEV1/FVC ratio correlated with raised incidence of new onset type 2 DM independent of BMI and smoking status.

Schnack et al.[68] mentioned that patients with type 1 diabetes mellitus had significant decline of FEV1, DLCO and vital capacity when compared with non diabetic patients.

Based on the evidences, COPD must be considered as a causative factor for the new onset diabetes mellitus.

Mechanisms of the association of COPD and diabetes mellitus

1. Inflammation and oxidative stress

Systemic inflammation is a common feature occurring in both COPD and T2DM, which drives insulin resistance, atherosclerosis and many systemic complications in patients with COPD. The occurence of generalised systemic inflammation is poorly understood in obstructive lung disease patients. It is a significant causative factor for obtaining many chronic diseases, which are

comorbidities of COPD.[69] There are several proofs that the range of inflammatory markers such as TNF- α, IL-6 and C reactive protein (CRP) are markedly elevated in patients with COPD during exacerbation. IL-6 levels have an independent association with COPD. Plasma levels of IL-6 was found consistently elevated in patients of COPD in acute exacerbation when compared with stable COPD patients.IL-1 is associated with the mechanism of inflammation in COPD.[70]COPD has an independent correlation with elevated levels of CRP. COPD is independently correlated with raised levels of TNF-α which may lead to activation of NF-kB leading to cytokine production, upregulation of adhesion molecules and increasing oxidative stress.

Coexistence of COPD and metabolic syndrome increases systemic inflammation causing exacerbation of both the diseases. In supporting this evidence, inflammation is very severe at all GOLD stages of COPD patients with diabetes mellitus.[71]

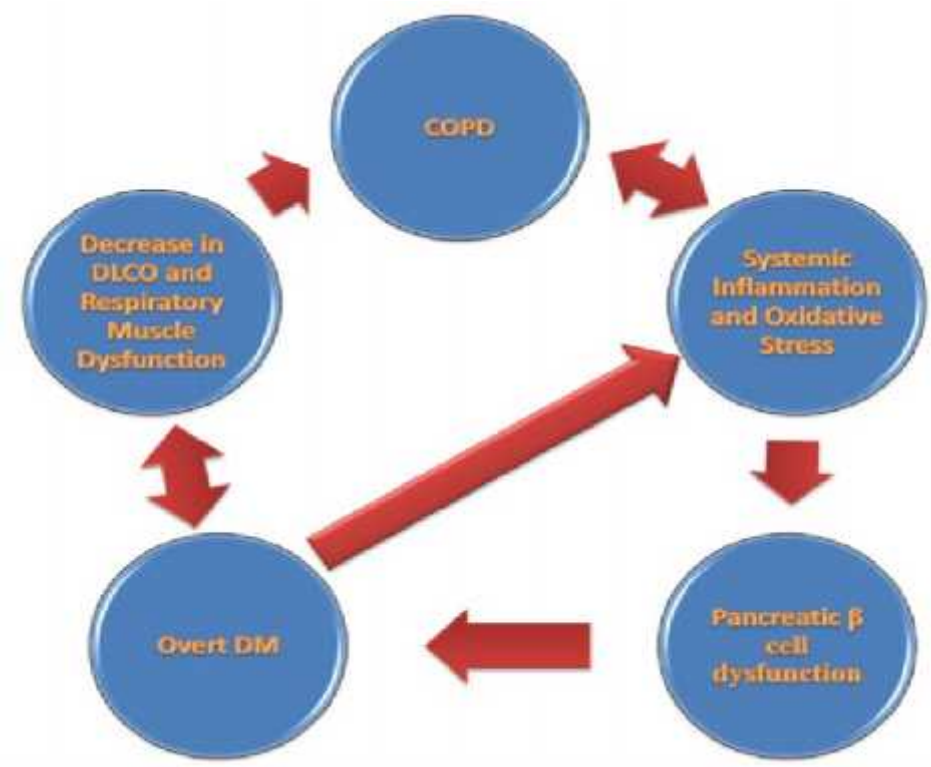
Altaranet al.[72] enrolled 50 patients with COPD to assess the association between IL-6 and COPD severity. They showed an increase in IL-6 among the patients with COPD and an independent association between IL-6 and airflow limitation.

Sprangeret al.[73] observed 27,548 individuals to analyse the association among inflammation and diabetes. In that study they found out that IL-6 and interleukin-1beta may be useful predictors of the development of new onset diabetes mellitus.

Bolton et al.[74] recruited 56 non-hypoxemic COPD patients and 29 healthy controls to study the potential association between inflammation and insulin resistance. Patients with COPD had higher insulin levels, which were related to inflammatory markers such as CRP, IL-6 and soluble receptors for TNF-α. Indeed, the

COPD related inflammatory state may underlie the pathogenesis of an increased risk of type 2 DM in these patients.

Figure 6. Relationship between COPD and diabetes mellitus



2. Hypoxia and glucose metabolism

Hypoxia induces strong metabolic reactions, necessitating a change in fuel preference to fatty acid oxidation from glucose.[75] In general population those who are healthy, at high altitude, altered insulin action in the liver occurs leading to increased gluconeogenesis and it is further accompanied by elevated insulin sensitivity and increased uptake of glucose in the skeletal muscle.[76] Blood glucose concentrations are lower at high altitude than at sea level.[77] During visit to high altitude, diabetic patients had improvement in metabolic profile and glycaemic control. By contrast, high-

altitude dwellers most probably have metabolic syndrome than sea-level dwellers.[78]Chronic hypoxia in COPD patients have contributed to intolerance of glucose [79] and raised lipolysis with altered sensitivity of insulin[80]. Expression of HIF-1α is elevated pancreatic β cell regions in hypoxic conditions.

Cheng et al.[81] showed that HIF-1α has significant and beneficial effects on pancreatic β cell function, and hypothesized that HIF-1α may be a novel target to improve the function of insulin producing cells.

3. COPD and obesity

Obesity is more common in chronic lung diseases especially in COPD and less severe lung diseases. In an American study, 54% of people with strength of 355 COPD patients were obese compared to 35% of the overall general public. 61% of 355 COPD patients attending cardiopulmonary rehabilitation, when compared with 32% matched controls had central obesity.[82] Obesity was more found in Global Initiative for COPD stage I and II (16% and 24%) than in GOLD stage IV disease (6%). In COPD patients, higher range of BMI correlated with increased fat deposition and altered insulin sensitivity.[83]

Steutenet al.[84] recruited 317 subjects with COPD to study the prevalence of weight distribution in COPD patients in a Dutch primary care setting. In the study, obesity was much more prevalent in patients with mild to moderate COPD (16-24%) disease than in severe disease (6%).

4. Physical inactivity

Patients with COPD usually have exercise intolerance and decresed physical activity compared with healthy subjects. In a review of 11 studies with activity monitoring, patients with COPD were active for 58% of the time and at 75% of the intensity of the normal healthy adults.[85] They were also observed with physically inactivity for greater duration than healthy subjects (82% versus 68% of time) and spent more duration on rest and less duration with physical activity than controls.[86]

. Watzet al.[87] found a relationship independent of impaired pulmonary function among physical inactivity and metabolic syndrome in COPD.Many other studies have observed a moderately significant correlation among FEV1 % and physical activity.

5. Cigaratte smoke

Tobacco smoke exposure is a principal causative factor for the initiation of pathogenic changes of COPD. Smoking is relatedwith raised waist–hip ratio indicates raised deposit of adipose tissue. Euglycaemicclamp studies mentioned that tobacco smoking alters the insulin sensitvity and reduced uptake of glucose in the skeletal muscles leading to hyperglycemia.[88]

Facchini et al.[89] observed that cigaratte Smokers had increased steady-state plasma concentrations of glucose inresponse to slow infusion of somatostatin, glucose and insulin on comparison withnonsmokers.

Smoking habit correlates with manifestations associated with the metabolic syndrome whichincludes low HDL cholesterol, high triglycerides and increased plasminogen activator inhibitor[90]. Several population studies have observed an increased rate of metabolicsyndrome insmokers than in non-smokers. For example in

US adolescents, 1.3% of non-smokers and 8.6% ofsmokers had metabolic syndrome.[91] Subjects who smoke 20cigarettes per day has more than 70% risk of developing diabetes mellitus.

Mechanisms of the association of smoking and metabolic control

The impacts of cigarette smoking on use of insulin and oral hypoglycaemic agents or blood glucose control in diabetes mellitus have been published only in a very limited number of articles. In a study of 114 smokers dosage of insulin and serum cholesterol levels were very much higher than when compared with 164 non smokers, in a manner of dose dependancy. HbA1c was not investigated in this study, but glucose levels in the urine and blood were almost similar in both the groups. This indicates that a higher dosage of insulin is required to attain similar glycaemic control in smokers when compared to non-smokers.[92]The mechanisms involved in insulin resistance through smoking are as follows.

a. Increased level of triglycerides and palmitate

Various metabolic variables like triglyceride concentration and lipid levels in blood were different among ex smokers and non smokers resulting in insulin resistance. Plasma triglyceride levels is presumed to be an indicator for insulin resistance. Increased triglyceride levels and palmitate levels indicates resistance of adipocyte insulin in smokers even after smoking cessation without any difference in insulin, catecholamines or glucagon between groups. Matching between palmitate appearance and disappearance happens in steady state in to peripheral tissues. The continuous increase in levels of these triglycerides and palmitate influence insulin resistance through effects on pancreas and skeletal muscle.

b. Increased IRS phosphorylation

During the time of active smoking, smokers will have greater phosphorylation of the insulin receptor substrate on comparison with non smokers. After cessation of smoking, phosphorylation of IRS 1 reduced among smokers. Among the diabetes and also in insulin resistant family member of diabetic patients basal inhibition occurs in IRS-1 which was suggested by many reports. These data indicate that inhibition of signaling of insulin can be a significant pathogenesis involved in it along with smoke exposure induced resistance of insulin in diabetes mellitus patients.

C. Increased skeletal muscle lipids

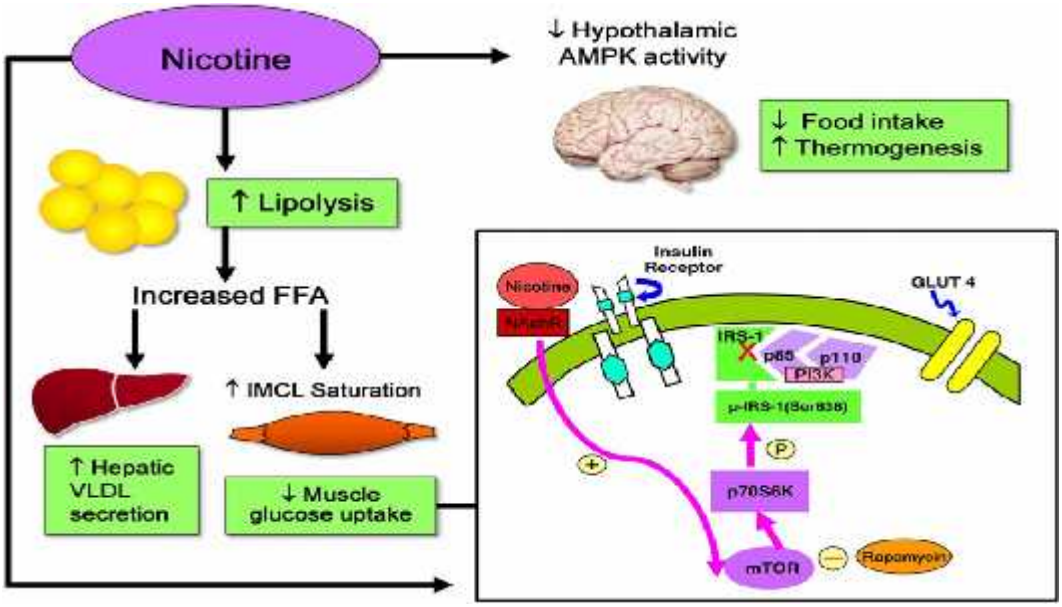
As per the studies, smoking could lead to increase in lipid concentration like plasma FFA and lipoprotein lipase of muscle without change in oxidation of fat and adipose tissue. This metabolic reaction might lead to changes in metabolism of lipids stored in skeletal muscle increasing resistance of insulin among smokers. Increase in acyl co-A and ceramide may also lead to insulin resistance. This is due to saturation of increased muscle lipids. Even after cessation of cigarette smoking, insulin sensitivity will not be normalized which is due to increased muscle lipids saturation.

D. Mammalian target of rapamycin activation

The mammalian target of rapamycin activation may be part of the integration of excess nutrient accumulation and insulin resistance. Mammalian target of rapamycin activation is a part of multisubunit serine/threonine protein kinase complex called Transducer of regulated CREB activity (TORC), that regulates major mechanisms including autophagy, apoptosis, protein synthesis and transcription. In cell culture, it is revealed that TORC is associated with basal inhibition of signaling of

insulin pathways among smokers. For smoking induced lung carcinoma, inhibitors of mammalian target of rapamycin activation were considered to play a significant role in its treatment..

Figure 7. Smoking induced insulin resistance



In cell culture, mammalian target of rapamycin activation and insulin receptor substrate 1 phopshorylation induced by nicotine were inhibited by rapamycin and it regularised sensitivity of insulin during the exposure of nicotine. Therefore, it proves that mammalian target of rapamycin activation has a significant role in the mechanism of resistance of insulin.

Treatment of COPD and the risk of hyperglycemia

COPD patients are consistently managed with steroids through either inhaled or systemic. Short-term oral and IV corticosteroid therapy for COPD patients in exacerbation is linked with a 5 fold raised risk of increased blood glucose levels.[93]Long-term steroid therapy in COPD patients without exacerbation is

associated with raised risk of impaired glucose intolerance.[94] Metabolic syndrome is consistent in increased endogenous steroids (Cushing's syndrome).[95]

Use of Inhaled corticosteroid for obstructive lung disorders in patients associated with diabetes mellitus correlated with a raised blood glucose levels, although the use might not have a significant effect on long term blood glucose control as assessed by glycatedhaemoglobin levels. Inhaled corticosteroids have much more favorable side effect profile, which is explained by the route of administration and a lower corticosteroid dose being administered. A recently published pooled analysis of 34 studies using inhaled steroids in patients with BA or COPD failed to show any association with new onset type 2 DM or hyperglycemia.

Effects of Diabetes mellitus on COPD

In people with COPD, diabetes is associated with, impaired pulmonary function, increased number of exacerbations andraised morbidity and mortality. Effects of metabolic syndrome on comorbidities of COPD includes skeletal muscle dysfunction, osteoporosis, increased risk of cancer and cognitive impairment which can be inferred from reviews in other patient groups.

1. **Effect of diabetes mellitus on pulmonary function**

In population studies, other than FEV1, metabolic syndrome is associated with reduced vital capacity in a restrictive pattern even after correction for confounding factors like smoking and others[96]. The mechanisms include increased systemic inflammation, mechanical and other effects of increased adipose tissue deposition leading to central obesity[97]. Lung diffusion capacity is reduced in patients with DM, with the greatest reduction in those with complications like microvascular

angiopathy.[98] Using electron microscopy, epithelial and endothelial capillaries of alveoli and basal laminar thickening in the lungs can be seen in people with diabetes. Microvascular disease in the pulmonary vessels may contribute to lung impairment in patients with both COPD and diabetes.

Researchers of Johns Hopkins University took 11,479 subjects free of type 2 DM and followed up for nine years. They found that lower FVC was independently associated with new onset type 2 DM in both men and women, independently from potential confounders such as age, weight and race.

Kwon et al.[99] studied that decreased FEV1 and FVC are directly associated with the new onset type 2 DM. The results are consistent even after adjustment for age, weight, health literacy and exercise.

2. Effect of diabetes mellitus on exacerbations

A study done by Kupeli et al.[100] analysed the correlation among acute exacerbations of COPD and metabolic syndrome. They found that 29 COPD patients matched for pulmonary function associated with metabolic syndrome had more number of exacerbations than 77 patients without metabolic syndrome in the follow up year. Duration of Exacerbation was more longerin metabolic syndrome and diabetes patients than in those without them.

COPD patients with diabetes mellitus have heightened risk of exacerbations and hospitalisation, more gram negative organisms in the sputum being cultured during exacerbation[101], and require longer stays in hospital.[102] At hospital admission, 50% of COPD patients develop hyperglycaemia.[103] Uncontrolled blood sugars during exacerbation is linked with greater number of pathogens grown on sputum culture and

non invasive ventilation (NIV) failure. Multiple mechanisms, including the pro-inflammatory effects of hyperglycaemia, impaired immunity and skeletal muscle dysfunction, are believed to play a vital role.[104] Hyperglycaemia may also increase the airway smooth muscle responsiveness on action with contractile agents.[105]

3. Effect on Mortality

There are currently very limited research works available that observed the relationship among DM and survival in patients with COPD. However diabetes mellitus predisposes to respiratory infections and cardiac disorders whichaffects more than 20% of patients with COPD. It is associated with elevated morbidity and mortality over5 years.[106]

Patients with both COPD and diabetes have elevated risk of mortality compared with those who have either of the two disorders. The risk of mortality is almost double among the patients with coexisting COPD and diabetes when with those without diabetes immediately after 24 months of hospitalisation for an exacerbation.[107] COPD confers a 27% larger risk of mortality on coexisting with diabetes mellitus.[108]

Effects on comorbidities

1. Respiratory muscle dysfunction

After 1 year, strength of skeletal muscle reduces by 4.3% in obstructive lung disease patients, compared with 1–2% in a healthy individual.[109] Muscle wasting in patients of COPD is a principal risk factor of mortality.Insulin resistance may be a vital mechanism paving the way for weakness and wasting of skeletal muscle in

patients of obstructive lung disorders associated with metabolic syndrome.Insulin resistance is associated with raised breakdown of muscle protein in nondiabetic and in patients with critical illness requiring dialysis.[110]

Insulin resistance contributes for mitochondrial dysfunction.[111] People with diabetes mellitus have decreased mitochondrial ATP production and its stimulation by insulin, specifying that insulin resistance may reduce fuel metabolism and mitochondrial activity leading to muscle weakness.

2. Osteoporosis

17–46% COPD patients have osteoporosis and 21–52% have metabolic syndrome.[112] Although there are currently no significant data available indicating the correlation between diabetes mellitus and osteoporosis in COPD, the two diseases are likely to be corelated at least by common factors such as smoking, physical inactivity, inflammation and corticosteroid treatment. Hypertension, a significant constituent of the metabolic syndrome increased LDL cholesterol and triglycerides are risk factors for low bone-mineral density and other features such as inflammation has a significant role in the mechanism of osteoporosis.[113]

Among the COPD patients, most of them have vitamin D deficiency[114] which in over several studies, has been corelated with higher risk of diabetes mellitus and metabolic syndrome or with increased severity of its issues. There is minimal data from prospective trials that vitamin D supplementation given for osteoporosis could serve useful for metabolic syndrome.

3. Depression

The prevalence of psychiatric disorders in COPD patients is 10–78%.[115]The mechanisms for depression are undoubtedly not simple, there is little data available from other groups that metabolic syndrome and diabetes mellitus could have a part in it. In a large meta-analysis, it was stated that people with metabolic syndrome were 26% highly prone to develop depression[116]. In an other study, age, fasting glucose and Hs-CRP were independently corelated with psychiatric symptoms, specifying that inflammation could play a role.[117]

4. Cognition

20% of people with COPD aged more than 45 years reported memory related and neurological problems.[118] Cognitive function testing signifies a specific pattern of impairment of cognition in people with COPD, with deficits of attention, execution and memory. Hypoxia, smoking and vascular disease are significant contributors for impairment of attention and memory decline in COPD. Metabolic syndrome may also play a role. In retrospective studies, metabolic syndrome and diabetes mellitus were independently corelated with cognitive impairment, except in those aged 80 years.[119]

5. Carcinoma

Both COPD and diabetes mellitus are related with a raised risk of cancer, even though it is inadequately known whether the amount of risk is raised again in people who have both the conditions.[120]Chronic inflammation could act as a significant role in the pathophysiology of carcinoma as a tumour growth promoter[121]. Apoptosis can

be inhibited by inflammatory markers which may interfere with cellular repair and increase angiogenesis, promoting metastatic invasion.[122]

Elevated blood glucose levels could be dangerous for COPD patients by driving infection, myopathy and inflammation. In COPD with exacerbation patients elevated blood sugar levels is related with increased probability of positive sputum cultures with pathogenic microorganisms leading to increased likelihood of respiratory tract infections.[123] Inflammatory markers like IL-6, TNF – α and IL -18 are raised by elevated blood glucose levels.[124]

In studies with mechanism optimal blood glucose control treated by insulin reduced inflammation and sepsis thereby reducing the ICU and hospital stay and requirement of antibiotics.[125,126,127] It is associated with reduced muscle catabolism. This is due to insulin which is a significant anabolic hormone which promotes stimulation of synthesis of protein post prandially.[128] Resistance of insulin is related with breakdown of proteins in the skeletal muscle in patients with normal blood glucose levels needing dialysis[129] and in patients of critical illness.[130]

Hyperglycaemia is often related with poor prognosis in various critically ill patients with pneumonia and ARDS and is very common in COPD patients particularly during exacerbations. They usually tend to have longer duration of hospital and ICU stay, increased risk of morbidity and mortality. However this association between hyperglycaemia and outcomes of COPD exacerbation patients has not been completely evaluated.

Although some evidences were there, still several large trials are required to assess the impact of hyperglycaemia on the outcomes of COPD patients in

exacerbation. Hence observing the shortage of evidences, this study has been taken up to assess the effects of hyperglycaemia on the course of treatment for COPD patients in exacerbation.

METHODOLOGY

A 12 month observational study was conducted in DR.PRABHAKAR KORE Hospital and Medical Research Centre, Belagavi.

Study design

Study design was a longitudinal observational study

Study period and duration

The study was conducted between January 2019 to December 2019 and the duration was one year.

Study place

The study was conducted in the department of Respiratory Medicine, KLES Dr. PRABHAKAR KORE Hospital and Medical Research Centre, Belagavi, a teaching hospital attached to KLE Academy of Higher Education and Research, Belagavi.

Sample size

The sample size was calculated with the minimum sample size

formula $n = \frac{Z\alpha^2 P(1-P)}{d^2}$

where P is the percentage of prevalence and d is the percentage likely difference in the prevalence. Zα is linked with the level of significance. For 5% level of the significance α = 1.96. The prevalence rate of DM among COPD group is 42.4%. With P = 42.4% and d = 25% of P, the sample size is calculated. The sample size of the study is 84.

Source of Data

Data were gathered from all the patients of COPD who were in acute exacerbation along with previously or newly diagnosed diabetes mellitus admitted under the Department of respiratory medicine, KLES Dr.PRABHAKAR KORE hospital and medical research centre, Belagavi over a period of one year.

Outcomes

Duration of hospital stay and rate of mortality were the primary outcomes. Duration of ICU stay, duration of treatment with non -invasive ventilation, invasive mechanical ventilation requirement, duration of treatment with intravenous corticosteroids and number of patients with requirement of more than 1 antibiotic were the secondary outcomes of the study.

Inclusion criteria

All the patients with COPD who were admitted for acute exacerbation along with previously or newly diagnosed diabetes mellitus will be included in the study.

Exclusion criteria

- Patients with old or active pulmonary tuberculosis infection.
- Patients with chronic lung disorders other than COPD.
- Patients with HIV and other immunosuppressive disorders.
- Presence of hypertension and other co morbidities other than diabetes mellitus.
- Presence of diabetic nephropathy and all other complications of diabetes mellitus.

Method of collection of data

All the COPD patients who were in acute exacerbation along with the newly or previously diagnosed diabetes mellitus were included in the study. COPD was confirmed based on the GOLD 2018 criteria which states the presence of post bronchodilator FEV1/FVC value < 0.70 and the spirometry value included was done prior to the study and not during the exacerbation. Patients were classified based on the Anthonisen's criteria for exacerbation of COPD. The Anthonisen's criteria is as follows.

Figure 8.Anthonisen's classification of exacerbation of COPD

Type I (most severe)	**Type II**	**Type III**
All three symptoms (i.e., Increased sputum volume, increased sputum purulence and increased dyspnea)	Any two symptoms present	One symptom present and atleast one of the following: An upper respiratory tract infection in the past 5 days, increased wheezing, increased cough, fever without an obvious source, a 20% increase in respiratory rate and heart rate above baseline

Patients with COPD in acute exacerbation are classified into Type I, II and III based on the above criteria. All the COPD patients with previously or newly diagnosed diabetes mellitus were included in the study. Diagnosis of diabetes mellitus was based on the American Diabetes Association criteria. The ADA criteria is as follows.

Figure 9. ADA Criteria for the diagnosis of diabetes mellitus

- Symptoms of diabetes plus random blood glucose concentration ≥ 11.1mmol/L (200mg/dl) or
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dl) or
- HbA1c ≥ 6.5%
- 2 hour plasma glucose ≥ 11.1 mmol/L (200mg/dl) during an oral glucose tolerance test

All the patients included in the study were admitted and treated for acute exacerbation of COPD and diabetes mellitus. They were evaluated in detail of their present symptoms, history of diabetes mellitus or other co morbidities, past history of tuberculosis and its treatment, smoking habits, usage of inhalers for COPD, exacerbation and socioeconomic history. Clinical examination was done and diagnosis was confirmed. All investigations mentioned below were performed.

Patients were classified into two groups based on the mean random blood glucose levels of the entire hospital stay period. RBS levels were checked thrice daily during the admission period and mean value was calculated from all the sugar levels. Patients with mean RBS < 250 mg/dl were included in group A. Patients with mean RBS ≥ 250 were included in group B.

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 as controlled and poorly controlled diabetic patients. Those with HbA1c < 7.5 were included in controlled diabetic patients group and those with HbA1c ≥ 7.5 were included in poorly controlled diabetic patients group. They were compared and analysed with the outcomes during the hospital stay

Investigations

- Complete blood count and S. Procalcitonin
- Blood renal and liver profile
- Chest X ray
- Fasting, post prandial and random blood sugars.
- HbA1C levels by Bio – rad D 10 Haemoglobin system.
- Urine routine and microscopy
- HIV, HBsAg and HCV
- Sputum for gram stain, culture and sensitivity.
- Arterial blood gas analysis

Ethical clearance

The ethical clearance was obtained from the Ethical and Research Committee, KLE Academy of Higher Education and Research, Belagavi before the initiation of the study.

Informed Consent

Before enrolment, all the patients who fulfilled the criteria were informed regarding the procedures of the study and their participation in it. After obtaining the written informed consent, patients were considered in the study.

Statistical analysis

For the continuous quantitative variables, mean and standard deviation will be calculated. For the use of comparison, if the data is classified into two groups with respect to certain qualitative characteristic, the continuous variables will be compared using the other suitable tools of statistics. Discrete variables will be represented by median. Suitable graphs will be 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 will be tested using test of proportion or Fisher's exact test. For all the tests the value of p less than 5% (0.05) will be considered significant.

RESULTS

The prospective observational study for 1 year was conducted inKLES DR.PRABHAKAR KORE Hospital and Medical Research Centre, Belagavi.

97 patients of COPD coexisting with Diabetes Mellitus were included in the study. 11 patients were excluded due to other chronic lung and cardiovascular diseases. 3 patients went against medical advice discharge during the study. So 13 patients were excluded and 84 patients were considered in the final analysis.

All the patients involved in the study were classified into two groups based on the mean random blood glucose levels during the hospital stay as group A < 250 mg/dl and group B ≥ 250 mg/dl. There were 40 patients in the group A and 44 patients in the group B included for the final analysis.

Mean age in the group A was 68.47± 8.20 and in the group B was 67.57 ± 11.74. The mean age of all the study patients were 68.00 ± 10.16. Majority of the patients were in the age group of 60 to 69 accounting for 50% of the group A patients and accounting for 40.91% of the group B patients.

Male patients were more in number accounting to 67.86% of the overall patients. In group A, the number of male patients was 28 (70%) and in group B, the number was 29 (65.91%). Mean BMI of the overall patients was 24.71 and mean BMI of the patients in group A was 23.9 whereas in group B, it was 25.45.

Considering the class of socioeconomic status, upper lower class had more number of patients among the study groups. In group A, 27.50% patients belonged to the upper lower class and in group B, 29.55% of the patients belonged to the same class. Upper class had the least percentage in group A and group B accounting up to

17.50% and 11.36% respectively. Meanwhile, upper lower class had highest percentage accounting up to 27.50% in group A and 29.55% in group B respectively.

Smokers were greater in number in the group A accounting up to 77.78% of the patients and accounting up to 83.33% in the group B. The overall percentage of the smokers among the study patients was 80.70%. The overall mean COPD duration was 5.15 ± 4.14 years, whereas in group A it was 5.57 ± 4.44 years and group it was 4.77 ± 3.86 years.

The overall mean FEV1% was 52.25% ± 10.28% and the mean FEV1% in group A was 52.87% ± 11.43% and in group B, it was 51.44% ± 8.81%. The mean FEV1/FVC ratio was 0.60 ± 0.05 in the group A and 0.62 ± 0.05 in the group B. The overall mean FEV1/FVC ratio was 0.61 ± 0.05 among the study patients. Around 9 patients in the group A and 19 patients in the group B had poor efforts during the interpretation. The above mentioned values were taken from the remaining 31 and 25 patients in group A and B respectively.

The number of patients who were on metered dose inhalers was 8 (20%) patients in group A and 11 (25%) patients in group B accounting to overall tally of 19 (23%) patients among the study groups.

Mean HbA1c in the overall patients was 7.87 ± 1.37. In the group A, the mean HbA1c was 7.20 ± 0.75 and in group B, it was 8.49 ± 1.52.

The overall diabetic mean duration was 5.65 ± 4.00 years and in group A, it was 4.28 ± 2.59 years and in group B, it was 6.57 ± 4.52. The number of patients on insulin for diabetic treatment in group A was 18 (45%) and in group B, it was 28 (63.64%) and the overall insulin usage among the study group was 46 (54.76%).

The leading cause of exacerbation was due to infection which was present in 14 (35%) patients in group A and 14 (31.82%) patients in group B. The overall leading cause of exacerbation among all the patients was due to infection which was present in 28 (33.33%) patients. The other causes were indoor pollution (11.90%), outdoor pollution (10.7%), irregular use of inhalers (15.48%) and unknown (21.42%).

Majority of the patients among the study groups belonged to the class II of Anthonisen's classification accounting up to 41 (48.81%) in number. Group B had more number of patients in class I accounting up to 17 (38.64%) patients whereas, group A accounting up to 7 (17.50%) patients. The exacerbation severity was higher in group B when compared to group A.

One of the significant findings in the study was that the 24 (28.57%) patients were newly diagnosed during the evaluation of the patients. Most of these patients had poorly controlled sugar levels and HbA1c $\geq$ 7.5. They were unaware of the poor glycaemic control.

Figure 10.Flow chart of the study patients

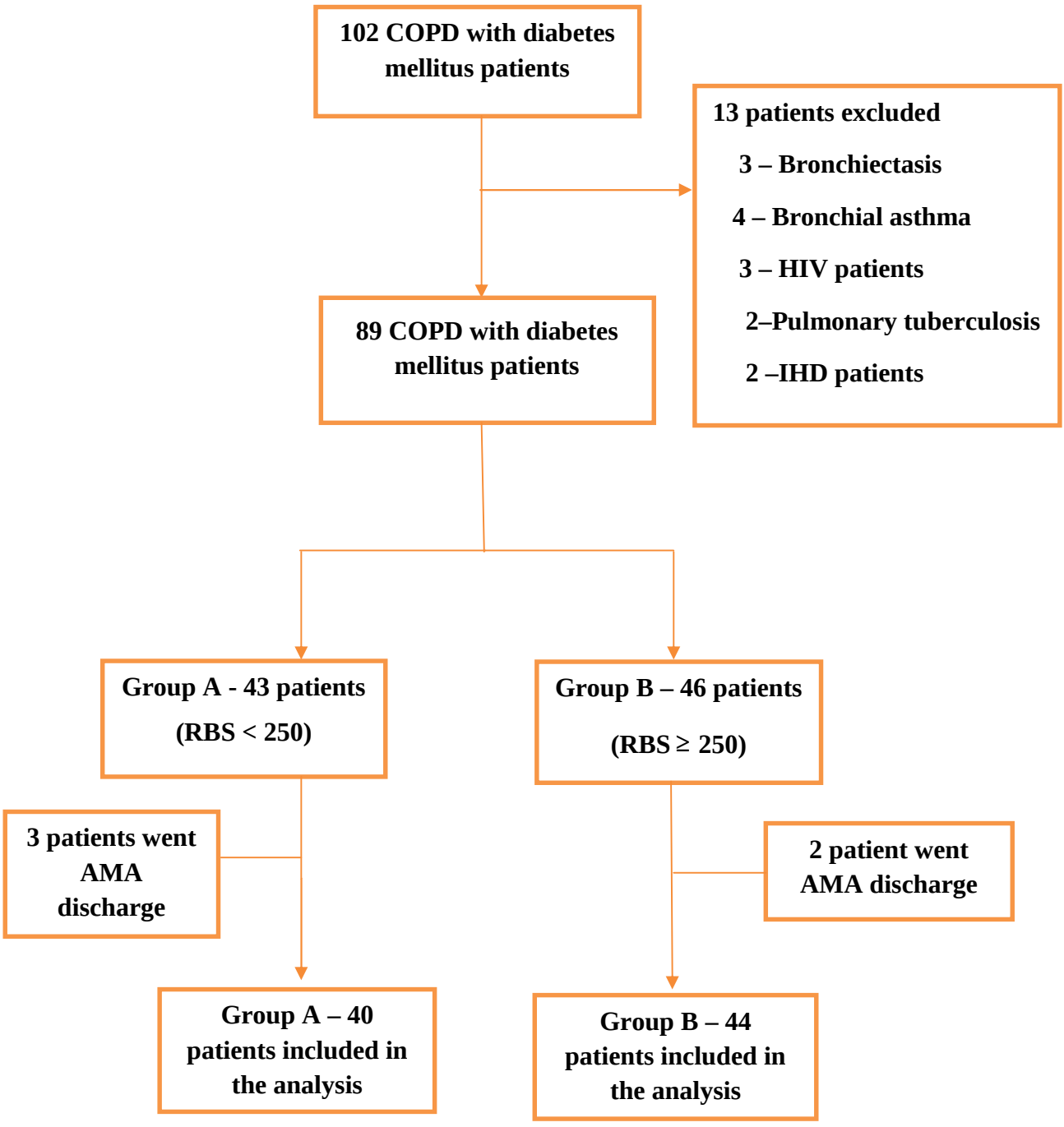


Table 1 - Baseline characteristics of the study patients

No. of patients	84
Age (mean ± SD)	68.00±10.16
Male sex	57 (67.86)
Female sex	27 (32.14)
BMI (mean± SD)	24.71±3.58
Smokers among males	46 (80.70)
FEV1% (mean ± SD)	52.25 ± 10.28%
FEV1/FVC (mean ± SD)	0.61 ± 0.05
COPD duration (years)	5.15 ± 4.14
No. of patients using MDI	19 (22.62)
HbA1c (mean ± SD)	7.87 ± 1.37
No. of patients using insulin	46 (54.76%)
Diabetes duration	5.64 ± 4.00

Among the study patients, meanage was 68.00 ± 10.16. 57 (67.86%) patients belonged to the male sex whereas 27 (32.14%) patients belonged to the female sex. Mean BMI was 24.71 ± 3.58. The number of smokers among male sex were 40 (47.62%). Mean FEV1% was 52.25 ± 10.28%.Mean HbA1c was 7.87 ± 1.37 among all the study patients.

Table 2. Comparison of the two groups with baseline characteristics

Characteristics	GROUP A	GROUP B
No. of patients	40	44
Age (mean ± SD)	68.475 ± 8.20	67.57 ± 11.74
Male sex	28 (70%)	29 (65.91%)
Female sex	12 (30%)	15 (34.09%)
BMI (mean± SD)	23.9 ± 3.88	25.45 ± 3.14
Smokers among males	21 (77.78%)	25 (83.33%)
FEV1% (mean ± SD)	52.87% ± 11.43%	51.44% ± 8.81%
FEV1/FVC (mean ± SD)	0.60±0.05	0.62±0.05
COPD duration (years)	5.57 ± 4.44	4.77 ± 3.86
No. of patients using MDI	8 (20%)	11 (25%)
HbA1c (mean ± SD)	7.2 ± 0.75	8.49 ± 1.52
No. of patients using insulin	18 (45%)	28 (63.64%)
Diabetes duration	4.28 ± 2.59	6.57 ± 4.52
Random blood sugar (mean ± SD)	225.00 ± 21.94	276.06 ± 12.08
Fasting blood sugar (mean ± SD)	183.38 ± 23.45	205.68 ± 24.06
Post prandial blood sugar (mean ± SD)	283.98 ± 34.09	334.83 ± 39.28

All the study patients were divided into two groups with 40 patients in group A and 44 patients in group B.

Mean age was almost similar in both the groups. Mean age value of group A was 68.47 ± 8.20 and group B was 67.57 ± 11.74. Similarly, sex distribution was equal in both the groups. Group A had 28 (70%) patients group B had 29 patients in the male sex.

The BMI value was 23.9 ± 3.88 in group A and 25.45 ± 3.14 in group B. Smokers among the male sex were almost similar in both the groups. Group A had 21(52.5%) smokers and group B had 19 (43.18%) smokers among the male sex.

The mean FEV1% in group A was 52.87% ± 11.43% and in group B, it was 51.44% ± 8.81%. The mean FEV1/FVC ratio was 0.60 ± 0.05 in the group A and 0.62 ± 0.05 in the group B.

Mean HbA1c among the overall patients was 7.87 ± 1.37. In group A, the mean HbA1c was 7.20 ± 0.75 and in group B, it was 8.49 ± 1.52. The overall mean duration of diabetes mellitus was 5.65 ± 4.00 years and in group A it was 4.28 ± 2.59 years and in group B, it was 6.57 ± 4.52 years.

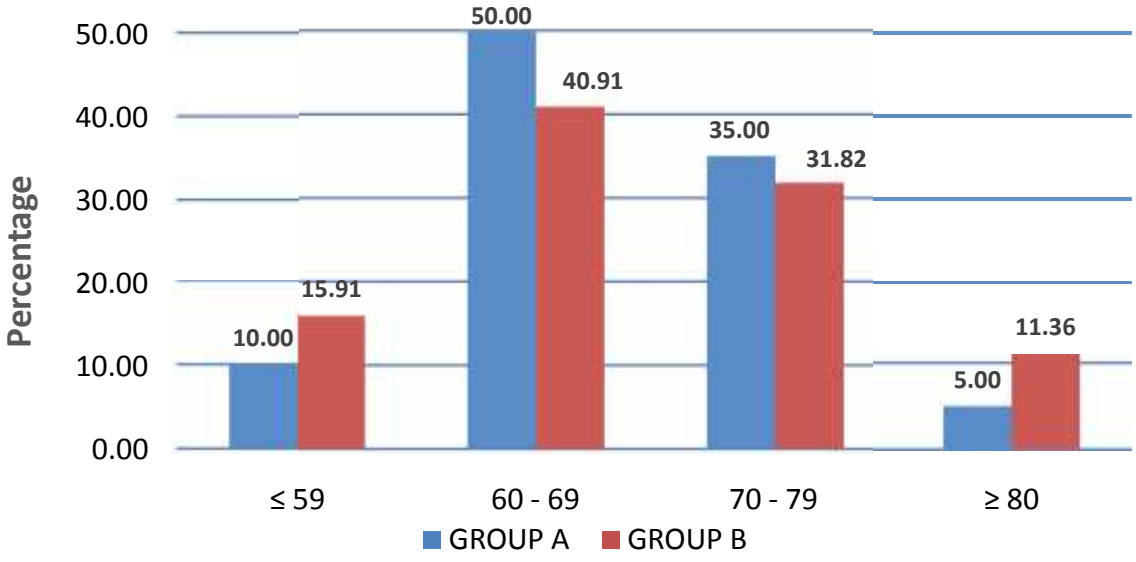
The mean random blood sugar levels among the overall study patients was 251.75 ± 30.99. The mean value of group A was 225.00 ± 21.94 and the mean value of group B was 276.06 ± 12.08.

The mean fasting blood sugar in the group A was 183.38 ± 23.45 and in group B, it was 205.68 ± 24.06. The overall mean fasting blood sugar was 195.68 ± 26.15. The mean postprandial blood sugar in the group A and group B was 283.98 ± 34.09 and 334.82 ± 39.28 respectively. The overall mean PPBS among the study patients was 310.06 ± 26.15.

Table 3. Age wise distribution among the study patients

	Group A		Group B		Total	
Age (years)	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
≤ 59	4	10.00	7	15.91	11	13.10
60 - 69	20	50.00	18	40.91	38	45.24
70 - 79	14	35.00	14	31.82	28	33.33
≥ 80	2	5.00	5	11.36	7	8.33
Total	40	100.00	44	100.00	84	100.00

Graph 1. Age wise distribution of patients in the two groups

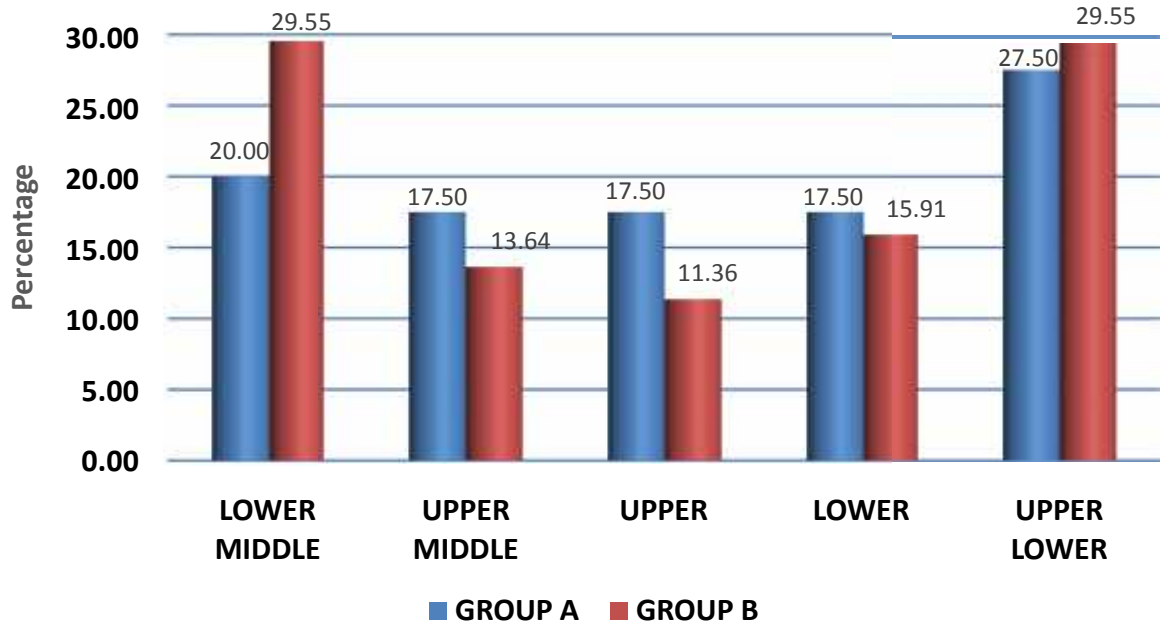


Majority of the patients were in the age group of 60 to 69 accounting up to 20 (50%) patients in group A and 18 (40.91%) patients in group B. Among the age group of 70 to 79, group A had 14 (35%) patients and group B had 14 (31.82%) patients.

Table 4. Socio economic status distribution among the two groups

	Group A		Group B		Total	
Socio economic status	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
Upper	7	17.50	5	11.36	12	14.29
Upper middle	7	17.50	6	13.64	13	15.48
Lower middle	8	20.00	13	29.55	21	25.00
Upper lower	11	27.50	13	29.55	24	28.57
Lower	7	17.50	7	15.91	14	16.67
Total	40	100.00	44	100.00	84	100.00

Graph 2. Socioeconomic status distribution among the two groups

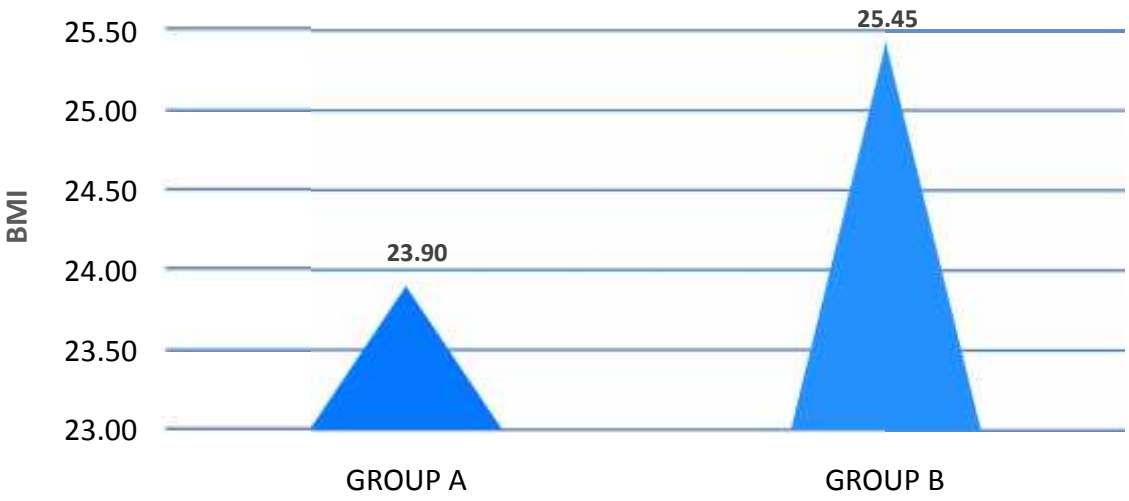


Upper lower class had more number of patients among the study groups.11 (27.50%) patients in group A and 24 (29.55%) patients in group B belonged to the upper lower class.

Table5. Comparison of mean BMI among the study participants

	Group A		Group B		Total	
	Mean	**S.D**	**Mean**	**S.D.**	**Mean**	**S.D.**
BMI	23.90	3.88	25.45	3.14	24.71	3.58
p value – 0.0461, Significant						

Graph 3. Comparison of mean BMI among the study participants

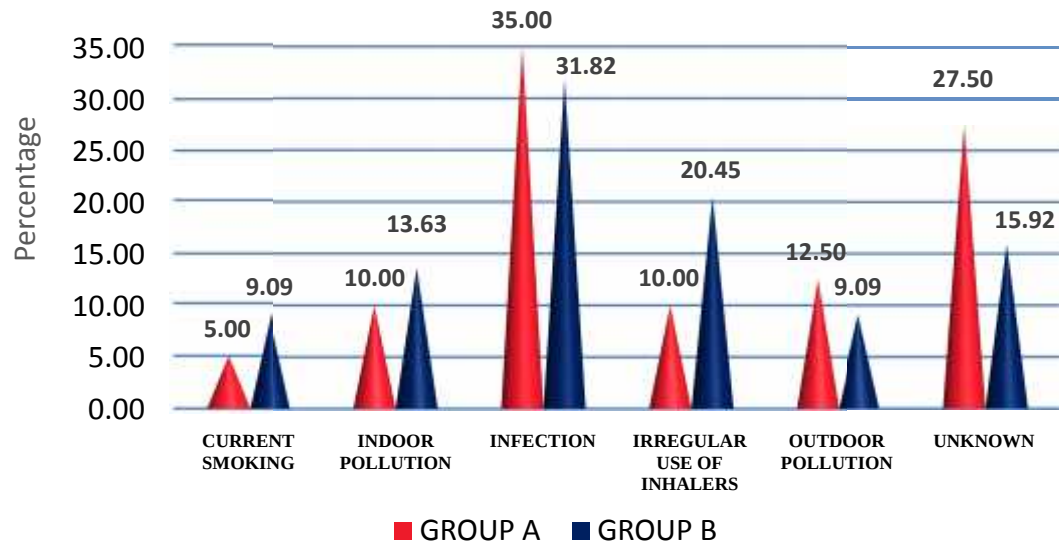


The mean BMI of patients in the group A was 23.90 ± 3.88 and group B was 25.45 ± 3.14 which was higher in group B. The mean BMI of all the patients in the study was 24.71 ± 3.58.

Table 6. Causes of exacerbation among the study patients

	Group A		Group B		Total	
Causes of exacerbation	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
Infection	14	35.00	14	31.82	28	33.33
Irregular use of inhalers	4	10.00	9	20.45	13	15.48
Indoor pollution	4	10.00	6	13.63	10	11.90
Outdoor pollution	5	12.50	4	9.09	9	10.71
Current smoking	2	5.00	4	9.09	6	7.14
Unknown	11	27.50	7	15.92	18	21.42
Total	40	100.00	44	100.00	84	100.00

Graph 4. Causes of exacerbation among the studypatients

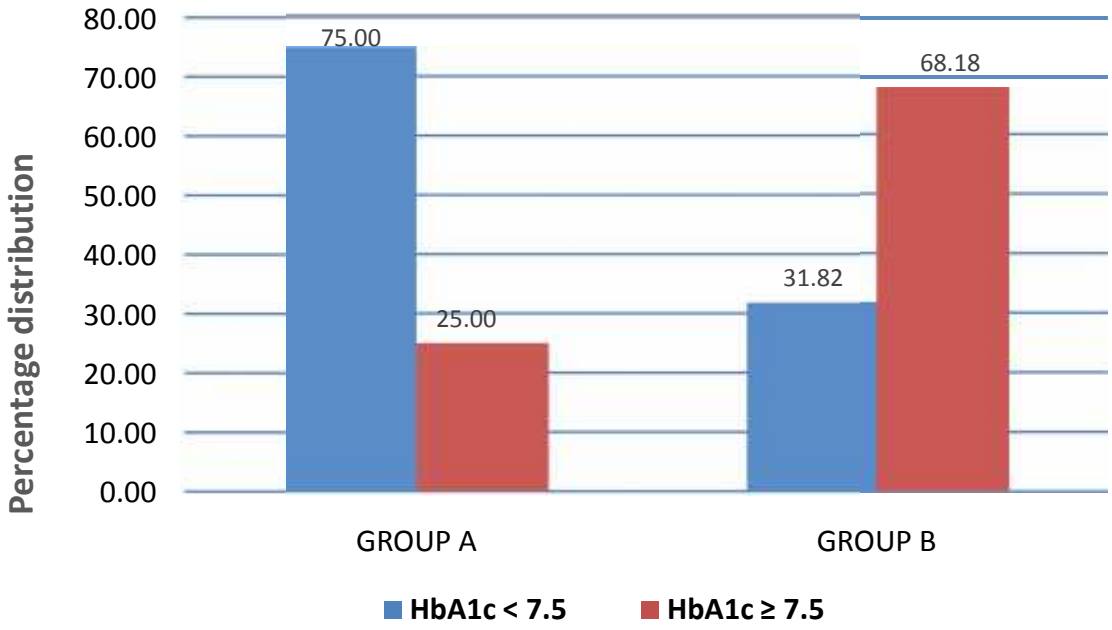


The leading cause of exacerbation was due to infection which was present in 14 (35%) patients in group A and 14 (31.82%) patients in group B. In overall, it was present in 28 (33.33%) patients. The other overall causes were indoor pollution (11.90%), outdoor pollution (10.7%), irregular use of inhalers (15.48%) and unknown (21.42%) among the study patients.

Table 7. Comparison of HbA1c among the study groups

	Group A		Group B		Total	
HbA1c	**No. Of patients**	**%**	**No. Of patients**	**%**	**No. Of patients**	**%**
< 7.5	30	75.00	14	31.82	44	52.38
≥ 7.5	10	25.00	30	68.18	40	47.62
Total	40	100.00	44	100.00	84	100.00

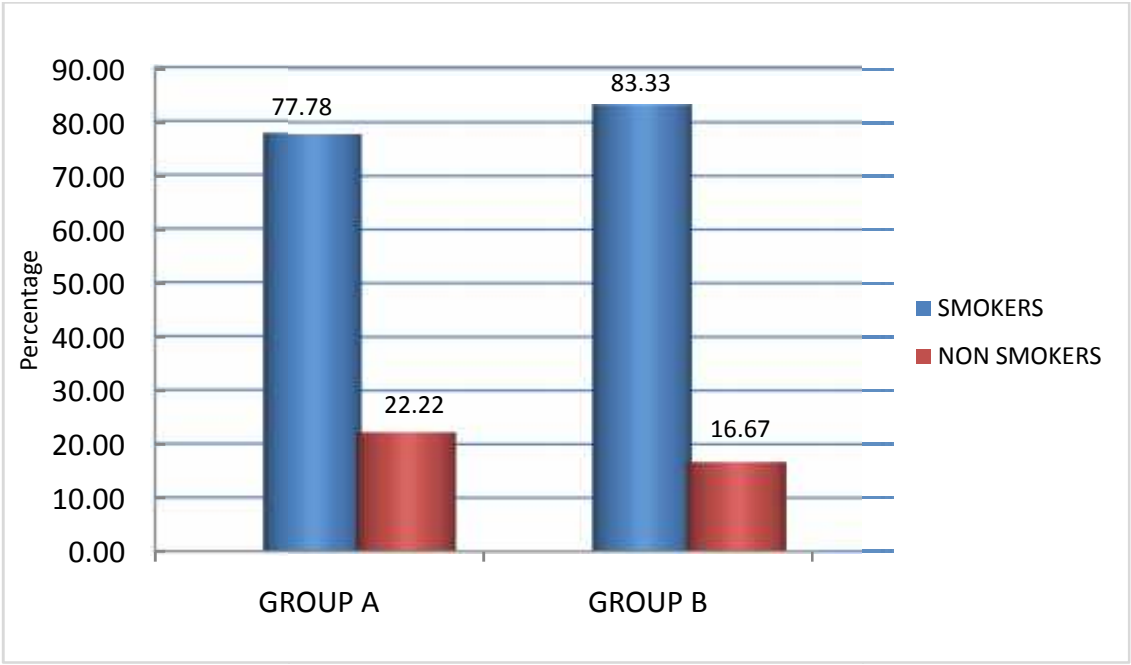
Graph 5. Comparison of percentage distribution of HbA1c among the study groups



Group A had 30 (75%) patients in the controlled group and 10 (25%) patients in the poorly controlled diabetes group. Group B had 14 (31.82%) patients in the controlled group and 30 (68.18%) patients in the poorly controlled diabetes group.

Table 8. Distribution of smokers among male sex in study groups

	Group A		Group B		Total	
Smokers among men	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
Smokers	21	77.78	25	83.33	46	80.70
Non smokers	6	22.22	5	16.67	11	19.30
Total	27	100.00	30	100.00	57	100.00

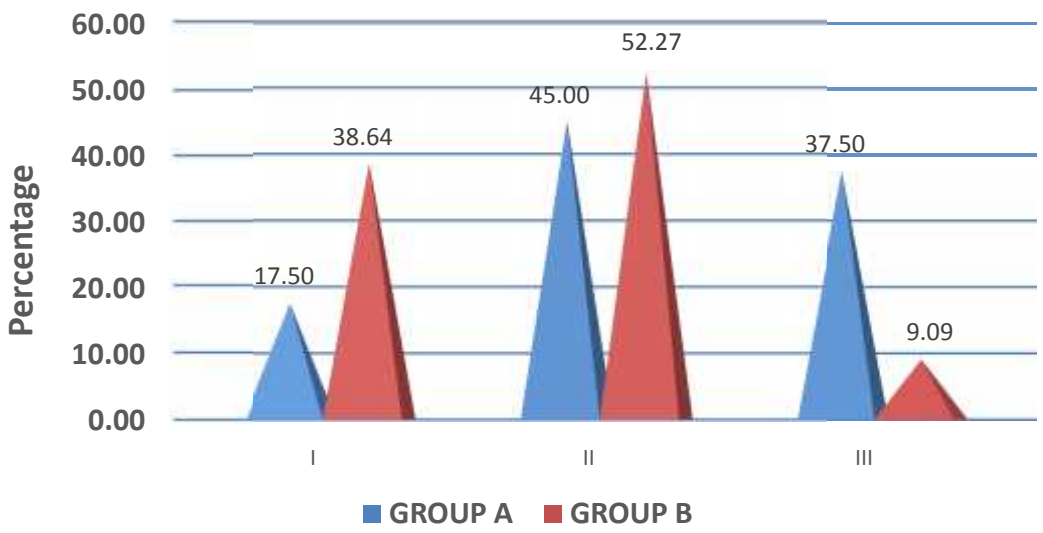


The number of smokers among male sex was 21 (77.78%) patients in group A and 25 (83.33%) patients in group B. The overall percentage of the smokers among male sex in the study patients were 80.70%

Table 9. Groups classified based on the Anthonisen's classification of COPD

	Group A		Group B		Total	
Class	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
I	7	17.50	17	38.64	24	28.57
II	18	45.00	23	52.27	41	48.81
III	15	37.50	4	9.09	19	22.62
Total	40	100.00	44	100.00	84	100.00

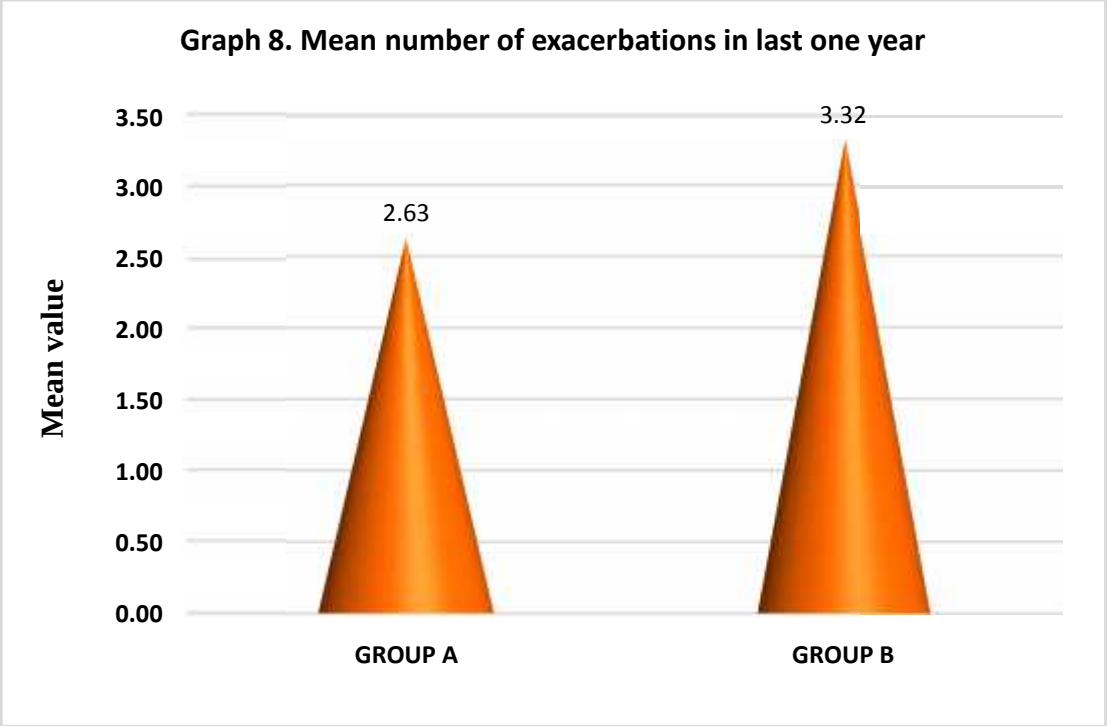
Graph 7. Percentage distribution of the study patients based on Anthonisen's classification of COPD



Most number of patients belonged to the class II accounting up to 41 (48.81%) in number. Group B had more number of patients in class I accounting up to 17 (38.64%) on comparison with group A of only 7 (17.50%) patients.

Table 10. Mean number of exacerbations in the last year among the study groups

	Group A		Group B		Total	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Number of exacerbations in the last one year	2.63	1.33	3.32	1.23	2.99	1.32
p value = 0.0154, significant						

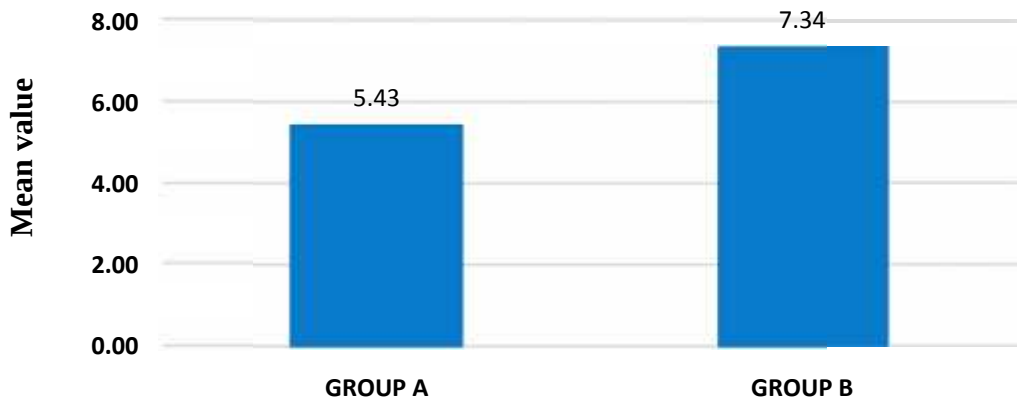


The mean number of exacerbations in the last 1 year was 2.63 in group A and 3.32 in group B. The total mean number of exacerbations was 2.99. The p value is 0.0154 which is significant.

Table 11. Comparison of mean duration of stay in the hospital among the study groups

	Group A		Group B		Total	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Mean Duration Of Hospital Stay (days)	5.43	1.71	7.34	2.82	6.43	2.53
p value = 0.0004, Significant						

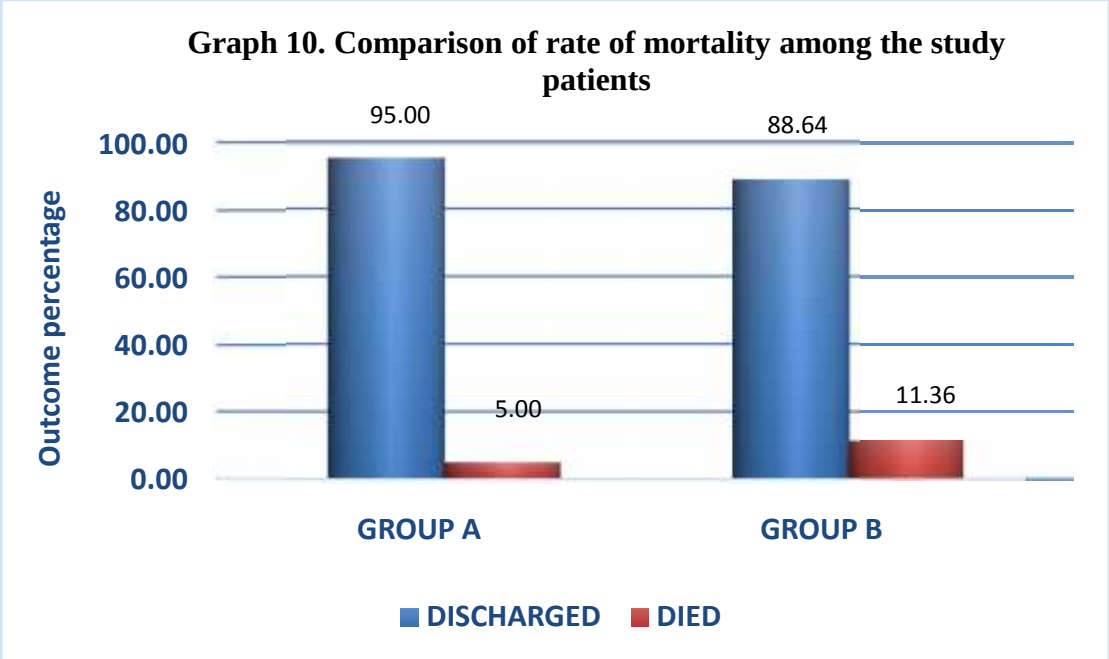
Graph 9. Mean duration of hospital stay (days)



The mean duration of stay in the hospital was higher in group B compared to group A. The mean duration in group A was 5.43 ± 1.71 days and in group B was 7.34 ± 2.82 days which was highly statistically significant. The total mean duration of all the patients in the study was 6.43

Table 12. Comparison of rate of mortality among the study groups

	Group A		Group B		Total	
Outcome	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
Discharged	38	95.00	39	88.64	77	91.67
Died	**2**	**5.00**	**5**	**11.36**	**7**	**8.33**
Total	40	100.00	44	100.00	84	100.00
p value = 0.2919, not significant.						

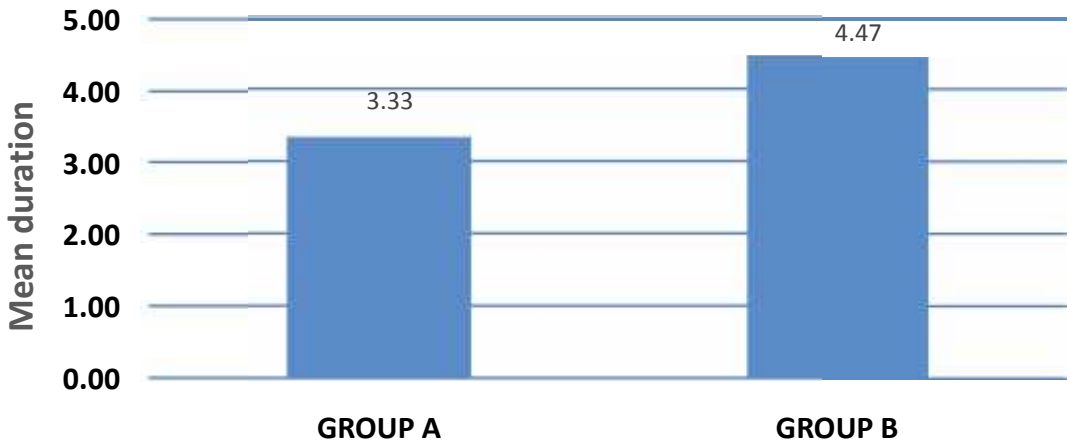


The rate of mortality in group A was 5.00 % and in group B was 11.36 %. The total number of patients expired was 7. The overall mortality of the study patients was 8.33%. The p value was not statistically significant.

Table 13. Mean duration of ICU stay among the study groups

	Group A		Group B		Total	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Duration of ICU stay (days)	3.33	1.12	4.47	1.60	4.04	1.52
p value = 0.0475, Significant.						

Graph 11. Mean duration of ICU stay among the study groups

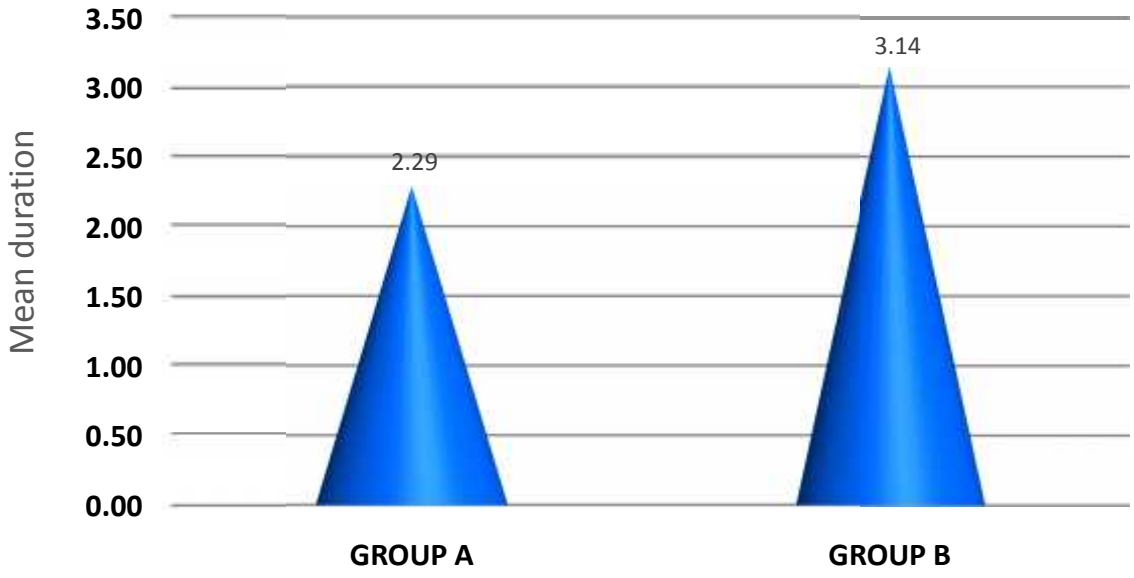


The mean duration of ICU stay in group A was 3.33 ± 1.12 days and in group B, it was 4.47 ± 1.60 days. Group B Patients had longer duration of ICU stay where as the p value(0.0757) was statistically not significant. The total mean duration of stay in the ICU is 4.04 ± 1.52 days. The p value was 0.0475 which is statistically significant.

Table 14. Mean duration of NIV days among the study groups

	Group A		Group B		Total	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Duration of NIV (days)	2.29	0.76	3.14	1.29	2.86	1.20
p value = 0.1240, Not significant.						

Graph 12. Mean duration of NIV days among the study groups

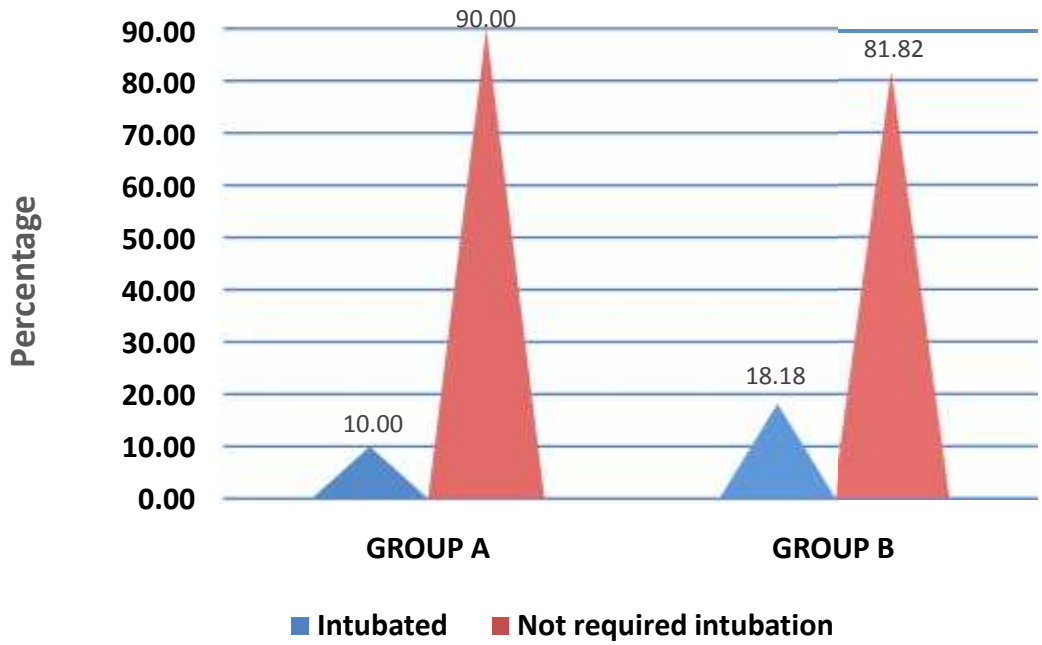


Mean duration of non invasive ventilation in group A was 2.29 ± 0.76 days and group B was 3.14 ± 1.29 days which was not statistically significant. The number of patients who were treated with NIV in group A was 7 and in group B, it was 14 which was double the number of patients in group A.

Table 15. Distribution of the intubated patients among the study groups

	Group A		Group B		Total	
Invasive ventilation	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
No. of patients who were intubated	4	10.00	8	18.18	12	14.29
No. of patients who do not require intubation	36	90.00	36	81.82	72	85.71
Total	40	100.00	44	100.00	84	100.00
p value = 0.2845, not significant						

Graph 13. Distribution of intubated patients among the study groups

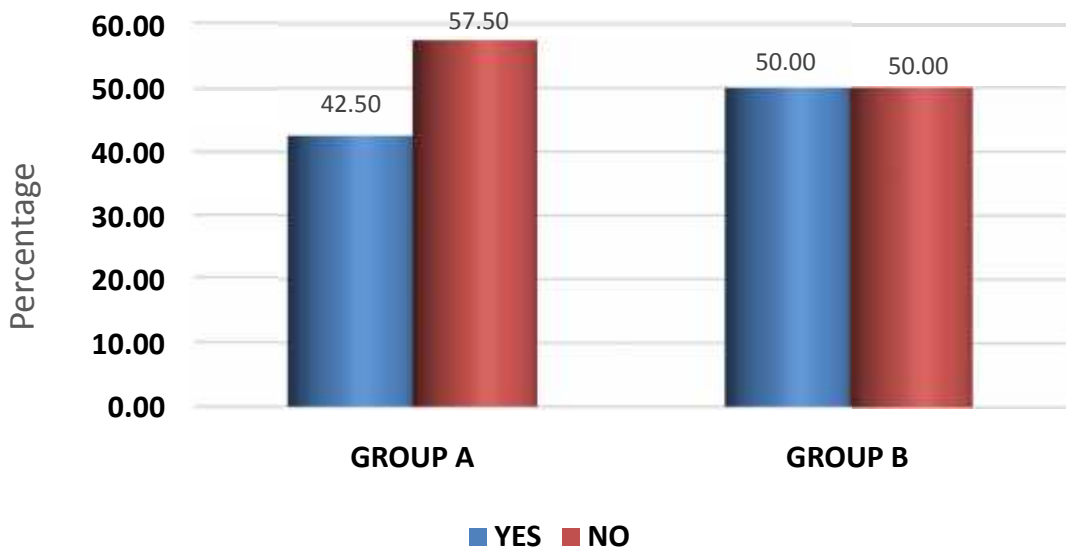


The number of patients who were intubated in group A was 4 (10%) and in group B was 8 (18.18 %). It was not statistically significant.

Table 16. Comparison of number of participants who received more than 1 antibiotic among the study groups

	Group A		Group B		Total	
>1 antibiotic	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
Yes	17	42.50	22	50.00	39	46.43
No	23	57.50	22	50.00	35	41.67
Total	40	100.00	44	100.00	84	100.00
P value = 0.5728, not significant.						

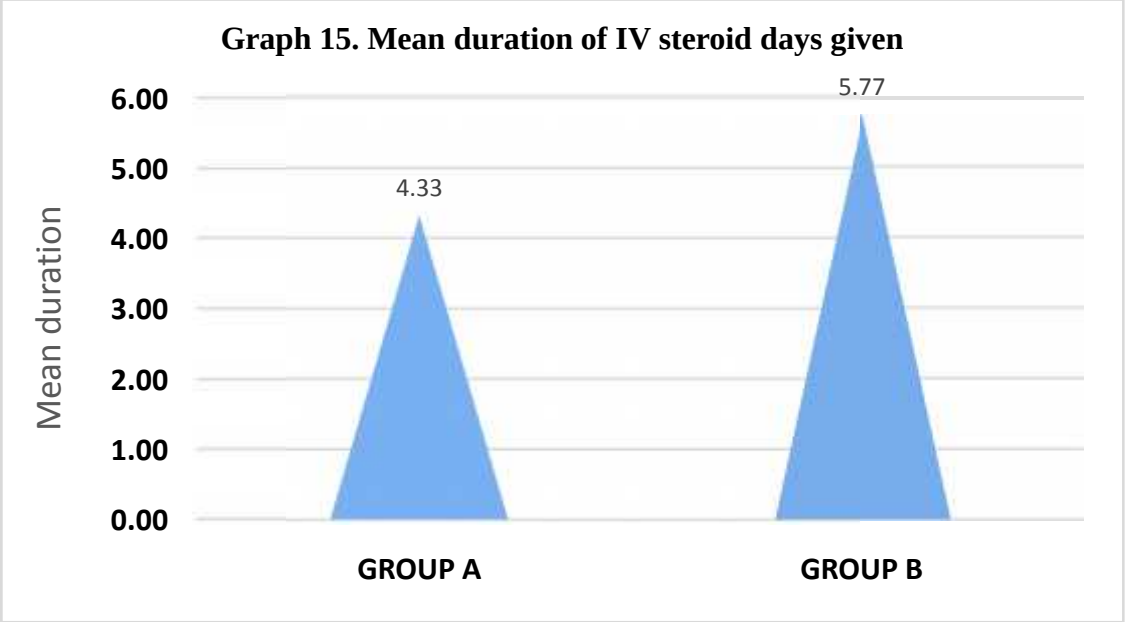
Graph 14. Percentage distribution of participants who received >1 antibiotic



The number of participants who received >1 antibiotic in group A was 17 (42.50%) and in group B was 22 (50%). The total number of patients who received >1 antibiotic was 39 (46.42%).The p value was not significant.

Table 17. Mean duration of IV steroid days among the study groups

	Group A		Group B		Total	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Duration of IV steroids given (days)	4.33	1.14	5.77	1.49	5.08	1.51
P value < 0.0001, Highly significant						

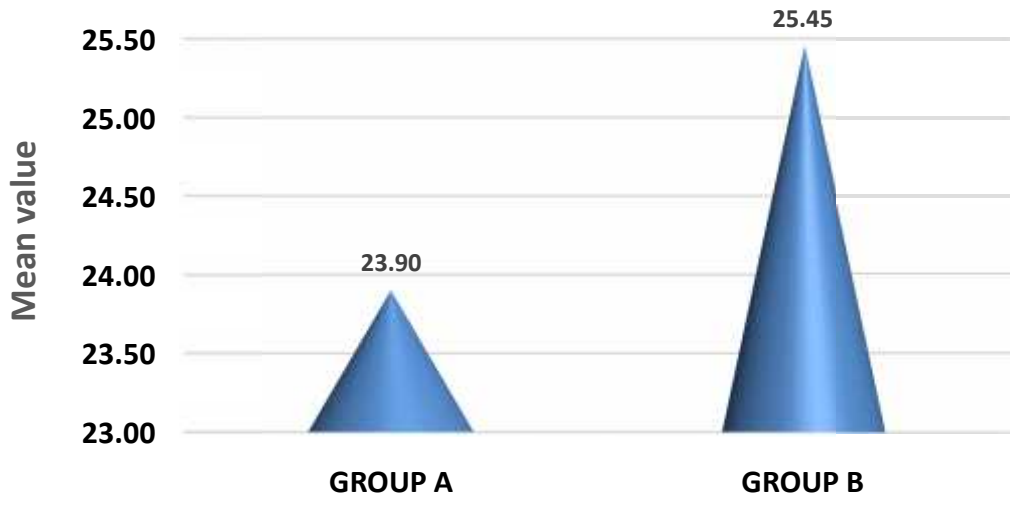


The mean duration of IV steroids given was 4.33 ± 1.14 days in group A and 5.77 ± 1.49 days in group B which had a highly significant p value of < 0.0001. The total mean duration of IV steroids given was 5.05 ± 1.51 days.

Table.18 Comparison of mean total WBC counts among the study groups

	Group A		Group B		Total	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Total WBC counts (10^3 / µL)	23.90	3.88	25.45	3.14	24.67	3.48
p value – 0.0461, Significant.						

Graph 16. Mean total WBC counts among the study groups



The mean WBC total count in group A was 23.90 ± 3.88, whereas in group B was 25.45 ± 3.14 with significant p value of 0.0461. The p value was 0.0461 which was statistically significant.

Table 19. Comparison of micro organisms grown in the sputum culture among the study groups

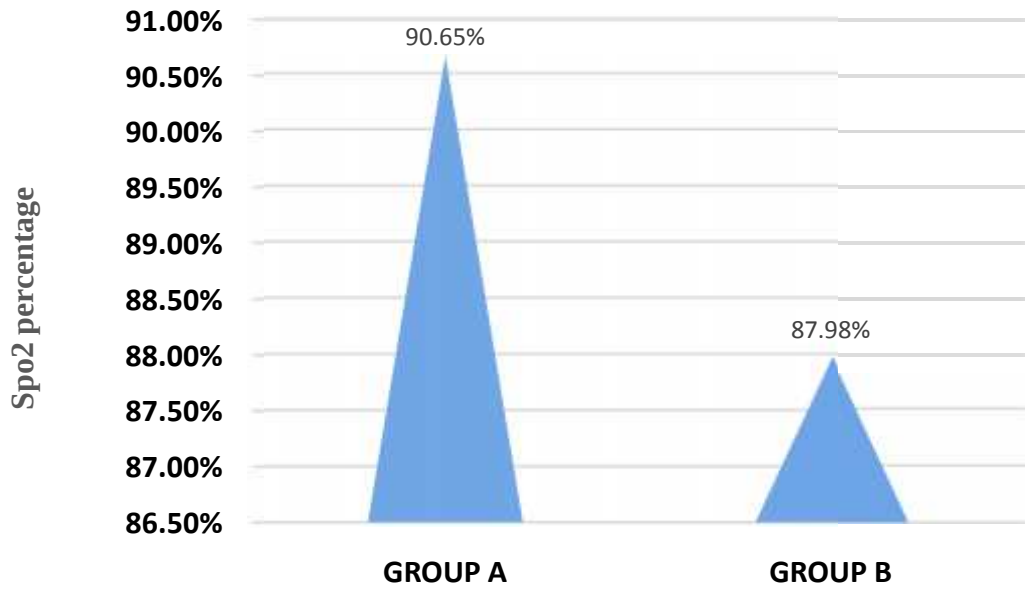
Sputum c/s	Group A		Group B		Total	
Organisms	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
Streptococcus pneumoniae	1	2.50	3	6.82	4	4.76
Haemophilus influenza	2	5.00	2	4.55	4	4.76
Klebsiella pneumoniae	2	5.00	1	2.27	3	3.57
Acenitobacter baumanni	0	0.00	2	4.55	2	2.38
Moraxella catarrhalis	1	2.50	1	2.27	2	2.38
Pseudomonas aeruginosa	0	0.00	1	2.27	1	1.19
No growth	20	50.00	20	45.45	40	47.62
Commensals	14	35.00	14	31.82	28	33.33
Total	40	100.00	44	100.00	84	100.00

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

Table 20. Comparison of mean saturation percentage among the study groups

	Group A		Group B		Total	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Mean Spo2 (%)	90.65	6.82	87.98	7.09	89.32	6.96
p value – 0.0826, Not significant.						

Graph 17. Comparison of mean Spo2 among the study groups

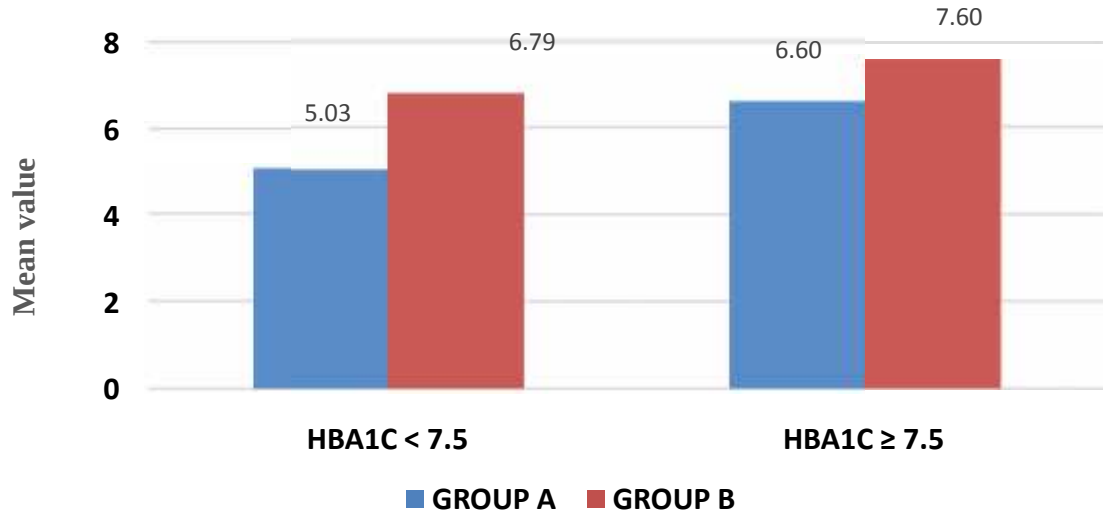


The mean Spo2 in Group A was 90.65 ± 6.82% and in group B was 87.98% ± 7.09%, whereas the p value was0.0826 which was not statistically significant**.** The overall mean Spo2 among the study groups was 89.31± 6.96%.

Table 21. Comparison of mean duration of hospital stay based on the HbA1c levels

	HbA1c < 7.5 (controlled) (days)		HbA1c ≥ 7.5 (days) (poorly controlled)		Total (days)	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Group A	5.03	1.35	6.60	2.17	5.43	1.71
Group B	6.79	2.64	7.60	2.91	7.34	2.82
Total	5.59	2.00	7.35	2.06	6.43	2.53
p value - < 0.0001, significant.						

Graph 18. Comparison of duration of hospital stay based on the HbA1c levels

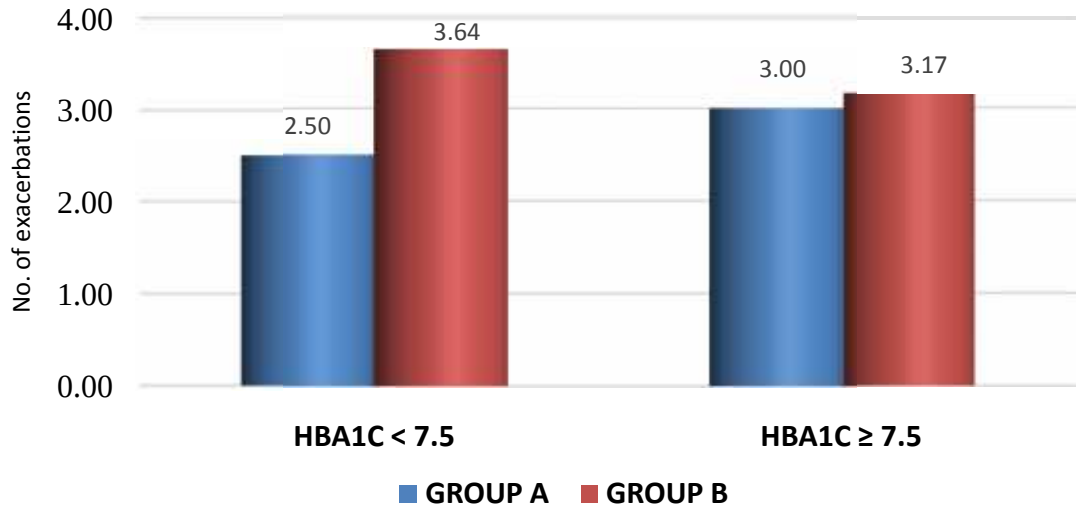


The mean duration ofhospital stay was higher in poorly controlled diabetic patients in both group A and B. The total mean duration of hospital stay in controlled diabetic patients was 5.59 ± 2.00 days and in poorly controlled patients was 7.35 ± 2.06days.The p value was < 0.0001 which was highly significant.

Table 22. Comparison of mean number of exacerbations in the last one year based on the HbA1c levels

	HbA1c < 7.5 (Controlled)		HbA1c ≥ 7.5 (poorly controlled)		Total	
Number of exacerbations in last one year	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Group A	2.50	1.31	3.00	1.41	2.63	1.33
Group B	3.64	1.28	3.17	1.21	3.32	1.23
Total	2.86	1.29	3.13	1.24	2.99	1.32
p value – 0.0154, significant.						

Graph 19. Comparison of mean number of exacerbations in the last year based on the HbA1c levels



The mean number of exacerbations in controlled group was 2.86 ± 1.29 and in poorly controlled group, it was 3.13 ± 1.24. The mean number of exacerbations were higher in poorly controlled group. The p value was 0.0154 which was statistically significant.

DISCUSSION

COPD is one of the foremost important causes of morbidity in the developing as well as developed countries. The contribution of India in prevalence of COPD is considered to be one of the greatest contribution in the world. The WHO estimates quote a figure of almost 5,56,000 deaths attributable to COPD in the Southern part of Asia which majorly comprises India. Thus, almost 95% of the mortality due to chronic respiratory diseases in India can be accredited to COPD. COPD is a systemic disease which is not only restricted to respiratory system but is also associated with co morbidities like diabetes mellitus, hypertension, osteoporosis etc.

Owing to its inflammatory pathology, COPD is thought to be a causative factor for developing insulin resistance leading to the onset of diabetes mellitus. 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 glycaemic control is considered as a significant causative factor which impairs lung function and induces structural changes thereby affecting it negatively. Hyperglycaemic status is linked with an increased risk of respiratory tract infections, frequent exacerbations and poor outcomes in patients with COPD. Alterations in carbohydrate metabolism are much more common in patients with COPD when compared to patients without COPD. So this study has been taken up to analyze the effect of glycaemic control in the outcomes of hospitalized COPD patients admitted with exacerbation.

The aim of the study was to assess the duration of stay in the hospital, rate of mortality and other outcomes of the acute exacerbation of COPD patients with hyperglycaemia.

A one year observational study was done in KLES DR. PRABHAKAR KORE Hospital and Medical Research Centre from January 2019 to December 2020.

All the patients involved in the study were classified into two groups and compared on the basis of mean random blood sugar levels during the stay in the hospital. 40 patients were allocated in group A and 44 patients were allocated in group B. The outcomes of the study were analysed and compared among both the groups.

Majority of the patients in our study belonged to the 60 to 69 age group with 45.24% of them in it, whereas it was 13.10% in the 50 – 59 age group. As age increases, the severity of exacerbation and blood sugar levels increases which may due to the increased insulin resistance as age increases. Male to female ratio was almost 2 : 1 indicating the male predominance in our study. 28.57% of the patients admitted among the study patients belonged to upper lower class in our study.

Usually, smoking worsens glycaemic control by affecting pancreatic beta cell function, fat metabolism and increase insulin resistance peripherally. In our study, 80.70% of the male patients were smokers. 83.33% were smokers among male in group B compared to 77.78% in group A.Maddattu and his colleagues studied over 40,000 male health care workers who were followed up twice a year had a relative risk of incident hyperglycaemia of 1.94 among those men in the workers who smoked > 25 cigarettes per day when compared with non smokers.

EPIC Norfolk study showed that raised blood glucose levels and poor glycaemic control correlated independently with cigarette smoking.[131] Compared to the above mentioned studies, there was no difference in both the groups in our study, but overall it has affected the glycaemic control.

The mean HbA1c in group A was 7.2 ± 0.75 and in group B it was 8.49 ± 1.52. 17.50% of the patients in group A and 38.64% of the patients in group B belonged to the class I of Anthonisen's classification. Majority of the patients in the class I (severe form) belonged to group B. It indicates the incidence of more severe exacerbations among the patients with uncontrolled blood sugars. This could have been due to the pro inflammatory nature of the COPD aggravated by elevated blood sugar levels causing recurrent and severe exacerbations. Along with inflammation, diabetes would have aggravated the exacerbations by increasing airflow limitation and reducing lung functions.

Ganet al.[132] showed that the risk of developing diabetes mellitus is linked with increased fibrinogen and other inflammatory markers. The proinflammatory nature of the disease may act as independent causative factor for exacerbations of COPD.

The overall mean exacerbation in the last one year in the controlled diabetes group was 2.86 ± 1.29 whereas in 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. To compare with the other studies, a study done by Kupeliet al[133] observed 106 COPD patients (29 with metabolic syndrome and 77 with no comorbidities) for 1 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. This correlates with our study and proves the direct correlation of glycaemic control and exacerbations.

Among the study groups, raised blood glucose levels were found in patients with severe exacerbations in group B which indicates the worsening of glycaemic control due to exacerbation and restricted physical activity associated with COPD. COPD being a pro inflammatory disease, due to release of inflammatory cytokines leads to altered insulin sensitivity. The cause of altered sensitivity can be due to oxygen radicals impeding the insulin signaling pathway. Increased lipolysis due to chronic hypoxia in exacerbation of COPD patients which may increase the insulin resistance and cause glucose tolerance impairment.

Bolton CE observed that increased peripheral resistance of insulin was higher in COPD patients when compared with healthy subjects. The cause was related to increased TNF α and IL-6 concentrations.[134]The relation between altered insulin sensitivity and persistent inflammation can be due to cytokine persuaded signaling of insulin receptor disruption.

Diabcare India 2011 study had observed around 6,000 diabetic patients and stated that the overall mean value of HbA1c in the study was 8.97 ± 2.2. Our study had lesser mean HbA1c value compared to the other mentioned studies. This may be due to the fact that our study had lesser sample size. Almost all the patients of COPD in our study were treated with corticosteroids in any of the routes such as inhaled therapy, oral and intravenous (systemic). This would have been most likely a cause of poorly controlled blood sugar levels in group B.

In a cross sectional study by Faulet al.[135] HbA1c values were elevated significantly even with inhaled corticosteroids after 6 weeks of fluticasone ICS treatment.

Barnes PJ observed higher blood glucose levels with ICS use in a dose dependant manner in patients of COPD coexisting with diabetes.[136] But in our study almost all the patients were on ICS out of which 52.4% of the patients belonged to the poorly controlled diabetes group indicating there was no significant correlation between ICS and glycaemic control.

Slatore et al.[137] showed that ICS with high dose were associated with minimal fluctuation in blood sugar levels but not a clinically significant raise to cause alteration in the therapy.

The overall mean FEV1% was 52.87% and 51.44% in group A and B respectively and the mean HbA1c in group A and B was 7.2 and 8.49 respectively. Both the groups had impaired lung function and poor glycaemic control which indicates that there is an association exists between lung function and optimal blood glucose levels. This is seen in a study by Fremantile which mentioned that poor glycaemic control was linked with lower FEV1, FVC and Vital capacity. In this study it was observed that gas exchange abnormalities and limitation of airflow were associated with severe exacerbations and morbidity among the COPD patients.

Habashyet al.[138] proved that the hyperglycaemic patients who were otherwise healthy had a substantial decrease in FEV1/FVC ratio, FEV1% and PEF. These studies stress on the information that poor glycaemic control is associated with reduced lung function.

The primary objective in our study was the mean duration of hospital stay which was 6.43 ± 2.53 overall. The mean duration of stay in the hospital in group B was 7.34 ± 2.82 whereas in group A it was 5.43 ± 1.71.The mean duration in poorly controlled diabetes group, it was 7.35 ± 2.06 and in controlled diabetes group was 5.59 ± 2.00. The mean duration of stay in the hospital was elevated among the patients with poor glycaemic control and it was much significant with a p value of < 0.0001. The possible explanation can be due to increased number of infections, severe excaerbations, sepsis leading to multiorgan dysfunction and uncontrolled blood sugar levels in group B. This might have lead to increased antibiotic and corticosteroid usage in those patients. Hyperglycemia further worsens infection in them by causing protein glycosylation, deranged function of leukocytes through its impairment and activation of pro-inflammatory genes through transcription factors.

Hospital acquired pneumonia was reported among 5 patients in group B which shows the impact of prolonged hospital stay and increased morbidity among the group B patients due to poorly controlled blood sugar levels.

The other explanation for the increased duration of hospital stay in poorly controlled diabetes group is that raised blood glucose levels would have caused impairment and worsening of the disease. The treatment with corticosteroids for exacerbation can further increase the blood sugar levels thereby, increasing the further complications.

Ferreira et al.[139] studied regarding the influence of glycaemic variation on duration of hospital stay and rate of mortality among the stable patients of COPD or community acquired pneumonia. The mean duration of hospital stay in the hospital was 10 days with >41% of the patients having HbA1c > 8.0%.

Alshabanat et al [140] observed the exacerbation of COPD along with diabetic patients numbered up to 1564 from around 6 hospitals in North America. They had a mean duration of hospital stay of 10.8 days.Compared to the mean duration in the above mentioned studies, our study had lesser mean duration even in poor glycemic control group which might be due to the lower sample size and reduced complications in group B.

Umpierrez GE et al.[141] mentioned in his study that hyperglycaemia is linked with a longer duration of stay in the hospital, elevated morbidity and increased complications whereas, optimal control of blood glucose levels of less than 150mg/dl decreased the antibiotic requirement and in hospital mortality.

Another primary outcome was the rate of mortality which was 11.36% in group B whereas it was 5.00% in group A. Even though it was not statistically significant, there was a relative increase in the rate of mortality in patients with poor glycaemic control in group B. Among the 84 patients in total, 7 of them died with the overall mortality rate of 8.33%.

The probable explanation may be due to the presence of increased severity of exacerbations, prolonged ICU stay infections with increased resistance to antibiotics and sepsis causing multiorgan dysfunction leading to death. The probable causative factor could have been the poorly controlled blood sugars promoting aggravated lung injury, inflammation leading to persistent hypoxaemia and worsening of the general condition. More commonly expected type of infection in hyperglycaemic patients is gram negative bacteraemia. The mortality rate in group B patients was double that of mortality rate in group A. Several studies conducted to look for the association between mortality rate and raised blood glucose levels had revealed that significant

association exists between them. COPD has a 28% higher risk of death when it coexists with diabetes mellitus.

Gudmundsson et al[142] mentioned in a study that out of 416 COPD patients, 122 patients had died during the follow up and the major cause of mortality was diabetes mellitus which was present in up to 16% of them. The rate of mortality was statistically significant with p value of 0.03.

Ahmed et al[143] found that among the COPD exacerbation patients admitted in ICU, the mortality rate was 11% in the group with diabetic patients whereas it was 4% in the non diabetic group.

Islam et al[144] showed that the mean random blood glucose levels of inhospital deaths among the acute exacerbation of COPD patients was 192 ± 97 whereas among the survivors the mean value was 151 ± 69.6. It stresses on the requirement of tight blood glucose control for all the patients to reduce the hospital stay and in hospital mortality.

In our study, the major cause of exacerbation was found to be 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, streptococcus pneumoniae and Haemophilus influenza were found each in the sputum culture of 4 patients. These were the 2 predominant organisms cultured. Klebsiella pneumoniae was present in 3 patients and Acenitobacter baumanni was present in 2 patients. No organisms or commensals were grown in most of the cultures.

Acute infections by viral or bacterial pathogens have been associated with development of COPD exacerbations. Prolonged use of inhaled steroids have also

been linked to development of pneumonia in COPD patients. Studies have shown that patients with poorly controlled blood glucose levels with prolonged usage of inhaled steroids have higher incidence of development of acute infections leading to increase in the rate of COPD exacerbations.

In our study the number of patients who received > 1 antibiotic in group A was 17(42.50%) and in group B was 22 (50%). The total number of patients who received > 1 antibiotic was 39 (46.42%). Although not statistically significant, the patients with poor control of blood glucose required more than one antibiotics. As per the data in our study, hyperglycaemia remained the significant cause of increased stay in the hospital and hospital acquired infections causing significant antibiotic requirement.

In our study, the mean duration of IV steroids usage was 4.33 ± 1.14 days in group A and 5.77 ± 1.49 days in group B which had a highly significant p value of > 0.0001. The total mean duration of IV steroids given was 5.08 ± 1.51 days. We observed the increased usage of steroids in our study and especially in group B. As severe exacerbations and lung damage were observed more among group B patients, their steroid doses were higher in them. This higher steroid dosage could have worsened the glycaemic control and also aggravated.The underlying mechanism could be due to derangement in beta cell dysfunction and persistent hyperglycaemia by altering the insulin sensitivity.

A study done by Niewoehner et al.[145] mentioned that treatment with systemic corticosteroids was associated with the development of medically relevant hyperglycemia in 271 patients with COPD exacerbation correlating with our study.

28.57% of the patients among the study groups were newly diagnosed with diabetes mellitus during the evaluation of the study. They were unaware regarding their diabetic status. This indicates the fact that COPD might be a causative factor for developing type 2 diabetes mellitus.

Fearyet al.[146] colleagues studied the medical records of more than 1 lakh patients retrospectively who were greater than 35 years of age. It showed an odds ratio of 2.04 for the occurrence of diabetes mellitus correlated with COPD.

It is important to screen all the COPD patients for impaired glucose tolerance and diabetes mellitus to reduce the risk of complications of diabetes at a later date.

In our study, we had observed increased duration of stay in the ICU among the patients in group B compared to group A. The mean duration of group B was 4.47 ± 1.60 days and the mean value of group A was 3.33 ± 1.12 days. Mean RBS in the group B was 276.06 ± 12.08 and mean value of group A was 225.00 ± 12.08. Poor glycaemic control in the group B correlates with the above data for increased duration of stay in the ICU. The mean duration of ICU stay among the study groups was statistically significant. This increase might have been due to the increased rate of infections, uncontrolled sugar levels and increased airway inflammation requiring continuous monitoring in ICU and prolonged recovery.

Increased corticosteroid use during the ICU stay could have been a more pronounced causative factor causing weakness of respiratory muscles. The neuromuscular weakness secondary to steroid induced myopathy should be considered as a principal factor for prolonged ICU stay in our study even though chest physiotherapy and rehabilitation were advised and given for all the ICU patients. Along with steroid use, hyperglycaemia would have been detrimental for our patients

by targeting, phrenic nerve function, diaphragm and other respiratory muscles which might have lead to prolonged recovery. Therefore, steroid use in the ICU should be provided accurately to minimize the complications.

Glycaemic variation increases oxidative stress, damages relaxation of vasculature which is endothelial mediated [and] increases inflammatory cytokine release.[147] It is also easily evident that tight glycaemic control in ICU could decrease the ICU stay and more importantly reduced incidence of hospital acquired pneumonia.

Archer et al.[148] showed that poor glycaemic control in the intensive care unit correlated with increased stay in the ICU and adverse outcomes in COPD patients who were in exacerbation particularly due to secondary infection. But the increased stay in the ICU was not statistically significant.

Mohammed et al[149] reported that among the acute exacerbation of COPD patients admitted in ICU, uncontrolled diabetes patients had an increased mean duration of ICU stay with value of 15.62 ± 11.33, whereas controlled diabetic patients had mean value of 12.13 ± 8.32 days of ICU stay which was statistically significant.

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

Chakrabarti et al.[150] showed that hyperglycaemia had poor impact on those patients with acute respiratory failure complicating COPD, thereby increasing the duration of ICU stay and NIV requirement. In their study, hyperglycaemic patients had increased NIV failure (33%) compared with normoglycemic patients(4%). In our

study, mean NIV duration in group B was 3.14 ± 1.29 and mean duration in group A was 2.29 ± 0.76. Although not statistically significant, there maybe a correlation between poor glycaemic control and increased duration of NIV requirement.

The number of cases intubated in group B was 8 (18.18%) and in group A, 4 (10.00%) patients required intubation. Again the number of intubated cases was on the higher side in group B compared to group A. This explains the aggravated overall lung function impairment during exacerbation due to hyperglycaemia.

Several studies had observed the correlation between reduced pulmonary function and mortality and stated that a 10% reduction in FEV1 was linked with a 13% increase in the all cause mortality. Hyperglycaemia is said to be linked with poor outcomes of the COPD patients and the worsening of the patient increases with the increase in RBS > 126 mg/dl which further contributes to various complications. The risk of death and duration of stay in the ICU increases at the rate of 10 – 15% for every 18mg/dl raise in plasma glucose levels.

In COPD patients with type II respiratory failure, initial blood glucose levels of > 200mg/dl was correlated independently with failure of NIV leading to increased risk of mortality. Higher blood glucose levels cause derangement in immune function and reduce chemotaxis, intracellular bacterial activity, opsonization, phagocytosis and cell-mediated immunity. These abnormalities tend to develop when glucose levels exceed 250mg/dl and do improve with glycaemic control.

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 had 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. This might have been caused by smoking and limited physical activity among the COPD patients. The observations from our study are poor NIV outcomes and increased rate of exacerbations were seen among the hyperglycaemic patients. In addition to it, the increased number of infections leading to sepsis and respiratory failure was seen more commonly among the uncontrolled diabetic patients.

The strengths of our study were longitudinal observational study, critically ill patients were observed in the study and it is the first kind of study to analyse the outcomes of the COPD patients in exacerbation based on their glycaemic control.

Limitations:

- The study was performed in a tertiary care centre. It might not represent the overall general population.
- Both controlled and poorly controlled diabetic patients classified based on HbA1c were included in group A and B. This might have influenced the outcomes among the study patients
- Group B had more number of patients in class I exacerbation which is more severe when compared to group A. This difference in severity might have influenced the results of the study.
- The confounding factors like secondary infection, use of corticosteroids might have extended the hospital duration.
- Spirometry values taken into consideration were obtained from the tests done in the last one year as it could not be performed during the exacerbation.

CONCLUSION

- COPD patients are highly prone to develop diabetes mellitus.
- The duration of stay in the hospital and rate of mortality were significantly increased in proportionate to the increased plasma glucose levels and in patients with poor glycaemic control.
- Hyperglycaemic COPD patients had increased severity of exacerbation and risk of infection.
- Poor glycaemic control in patients with exacerbation of COPD and sepsis had increased NIV failure leading to intubation and poor outcomes in the ICU stay.
- Strict glycaemic control, good physical activity and regular screening of COPD patients for diabetes mellitus and cessation of smoking along with regular use of inhalers will help in reducing the exacerbations and hospital admissions.
- In future, more studies are required for evaluation of the cause of poor outcomes for these patients at the molecular level to reduce the mortality of these two diseases.

SUMMARY

- The study was performed in a tertiary care hospital in Belagavi.
- Among the study 40 patients had RBS < 250 mg/dl and 44 patients had RBS ≥ 250 mg/dl. They were divided into group A and B respectively.
- 24 patients were diagnosed as diabetes mellitus newly during the screening of our study.
- Majority of the study patients were male sex (67.86%) and mean age was 68 ± 10.16
- Smokers were higher in group B which has 83.33% among compared to group A which has 77.78%.
- The overall mean FEV1 was 52.25% ± 10.28% and the mean value in both the groups were almost similar. There was no significant variation in both the groups.
- Major part of the participants belonged to the upper lower class in socioeconomic status among the study groups.
- The mean HbA1c in group A was 7.20 ± 0.75 and in group B it was 8.49 ± 1.52. The p value is < 0.0001 which is highly significant for duration of stay in the hospital.
- The leading cause of exacerbation was due to infection which was present in 33.33% of total study patients.
- The exacerbation was more severe in the group B compared to group A where they had majority of patients in class I and II.
- The mean duration of stay in the hospital was 6.43 ± 2.53 days overall, in group A, it was 5.43 ± 1.71 days and in group B it was 7.34 ± 2.82 days which was statistically significant.

- The mean value of the number of exacerbations among the study patients was 2.99 ± 1.32 years whereas it was higher in the group B with 3.32 ± 1.23 years.
- The rate of mortality was higher in group B with 5 (11.36%) patients contributing to total mortality of up to 7 (8.33%) patients.
- The mean duration of stay in the ICU among the study groups was 4.04 ± 1.52 days whereas it was higher in the group B with 4.47 ± 1.60.
- Mean NIV duration among the study groups was 2.86 ± 1.20 and it was not statistically significant among the study groups.
- The number of patients who received >1 antibiotic was 39 (46.43%) among the study groups. It was higher in group B with 50.00% of the patients treated with >1 antibiotic.
- Mean duration of IV steroid days was 5.08 ± 1.51 among the study groups with higher mean value of 5.77 ± 1.49 in group B which was statistically significant.
- Streptococcus pneumoniae (4.76%) and Haemophilus influenza (4.76%) were the predominant microorganisms grown in the sputum culture analysis.
- The study participants were classified into two groups based on the HbA1c cut off of 7.5 into controlled and poorly controlled diabetic patients.
- Poorly controlled diabetic patient group had more length of hospital stay which was 7.35 ± 2.06 and increased number of exacerbations with mean value of 3.13 ± 1.24 in the last year, which is statistically significant.
- Our study enlightens the need for proper glycaemic control and the poor outcomes associated with the poor glycaemic control.

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ANNEXURE I

ETHICAL CLEARANCE CERTIFICATE

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed - to-be- University)
Accredited "A" Grade by NAAC (2nd Cycle) Placed in Category "A" by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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Ref: MDC/DOME/ 31 **Date: 24/11/2018**

To,

Reg no- BR0118002
PG student in Respiratory Medicine,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"EFFECT OF HYPERGLYCEMIA ON DURATION OF HOSPITAL STAY AND RATE OF MORTALITY IN PATIENTS ADMITTED WITH ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE – AN ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

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ANNEXURE II

INFORMED CONSENT

TITLE OF THE STUDY: "EFFECT OF HYPERGLYCEMIA ON DURATION OF HOSPITAL STAY AND RATE OF MORTALITY IN PATIENTS ADMITTED WITH ACUTE EXACERBATION OF COPD – A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY"

PRINCIPAL INVESTIGATOR: Reg no- BR0118002

GUIDE: DR._____.

INTRODUCTION AND PURPOSE:

The research is intended to study the effect of poor glycemic control on the severity of Chronic Obstructive Pulmonary Disease and to know the impact of diabetes mellitus on its treatment outcomes. The main purpose of this study is to highlight the need for increased attention for the treatment of COPD patients in exacerbation with diabetes mellitus.

PROCEDURE:

I request you to kindly participate in the study titled: "**EFFECT OF HYPERGLYCEMIA ON DURATION OF HOSPITAL STAY AND RATE OF MORTALITY IN PATIENTS ADMITTED WITH ACUTE EXACERBATION OF COPD – A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY"**at Dr.Prabhakar Kore hospital and Medical Research Centre, Belagavi is being conducted by **Reg no- BR0118002**, post graduate in Department of Respiratory medicine at Jawaharlal Nehru Medical College Belagavi, Karnataka.

I request you to participate in this study as you are eligible to be included. During the study you will be asked questions regarding your present and past medical history and you will be required to answer to the best of your knowledge. Investigations including chest x-ray, sputum and blood investigations will be done. Your vitals will be noted. Outcomes and prognosis during this admission will be analysed.

If you agree to participate in the study, please furnish the details pertaining to the study.

RISKS AND BENEFITS:

No risk as such. No direct benefits, but the results of the study will help in the management of patients of Chronic Obstructive Pulmonary Disease in exacerbation with Diabetes mellitus

ALTERNATIVES:

If you are not willing to take part in the study, his / her treatment or any other further investigations the patient wants to undergo, in future, in KLE will not be affected by his / her decision.

VOLUNTARY PARTICIPATION/WITHDRAWAL:

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part and you can later change your mind and withdraw from the study. your decision will not change the present or future health care or other services that you receive. The study doctor or the sponsor may stop your participation in this study. I will tell if any important new findings that may change your willingness to continue to take part. If you choose not to

take part in the study you will receive the standard treatment for patients with your condition.

PAYMENT FOR PARTICIPATION:

No incentive will be paid to you for participating in this study.

COMPENSATION:

In the event that you become injured as a result of taking part in this study, treatment whatever available at KLE Dr.Prabhakar Kore hospital and Medical Research Centre, Belagavi will be offered to you. No reimbursement, compensation or free medical care is given.

CONFIDENTIALITY:

All information collected about you during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

AUTHORIZATION TO PUBLISH THE RESULTS:

The result of the study will be forwarded to the KAHER, Belagavi as part of the requirement towards the completion of MD degree, review and publishing.

If you/your relative have/has any questions about this study, you/your relative may contact, Institutional Ethical Committee for Human Subjects Research, Jawaharlal Nehru Medical College, Belgaum, Ph. 0831 2471350. You/your relative will be given a copy of this consent form for your/your relative's information and records.

CONSENT TO PARTICIPATE IN RESEARCH STUDY

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicated that I have read this entire consent form or it has been read to me, and had all my questions answered. I will be given a copy of this consent form.

Signature of the Participant or legally authorized representative:

Participant's Name :

Signature :

Name of legally authorized representative:

Signature :

Witness' Name :

Signature :

Investigator's Name

Signature :

Date and Place :

ANNEXURE III

PROFORMA

Name : BMI :

Age : IP NO :

Sex : Socio economic class :

Chief complaints :

K/C/O Diabetes Mellitus - yes / no

Duration of Diabetes Mellitus –

Treatment of diabetes Mellitus –

Probable cause of uncontrolled DM -

Duration of COPD -

No. of exacerbations in last one year -

Use of regular inhalers – yes / no

Use of MDI – yes / no

LABA ICS + LAMA or LABA ICS alone -

Use of LTOT at home -

PFT - FEV1/FVC – FEV1 % -

Ex smoker / current smoker / Non smoker

Probable cause of exacerbation -

Anthonisen classification – class I / II / III

Clinical examination :

On admission, Conscious / oriented

PR – BP –

SPO2 – RS –

RR -

Investigations :

HbA1c -

Mean RBS - FBS - PPBS -

Total counts -

S. Procalcitonin -

Sputum C/S -

CXR –

ABG –

Duration of ICU stay –

Duration of NIV –

Duration of Invasive mechanical ventilation –

No. of antibiotics required –

No. of days IV steroids given –

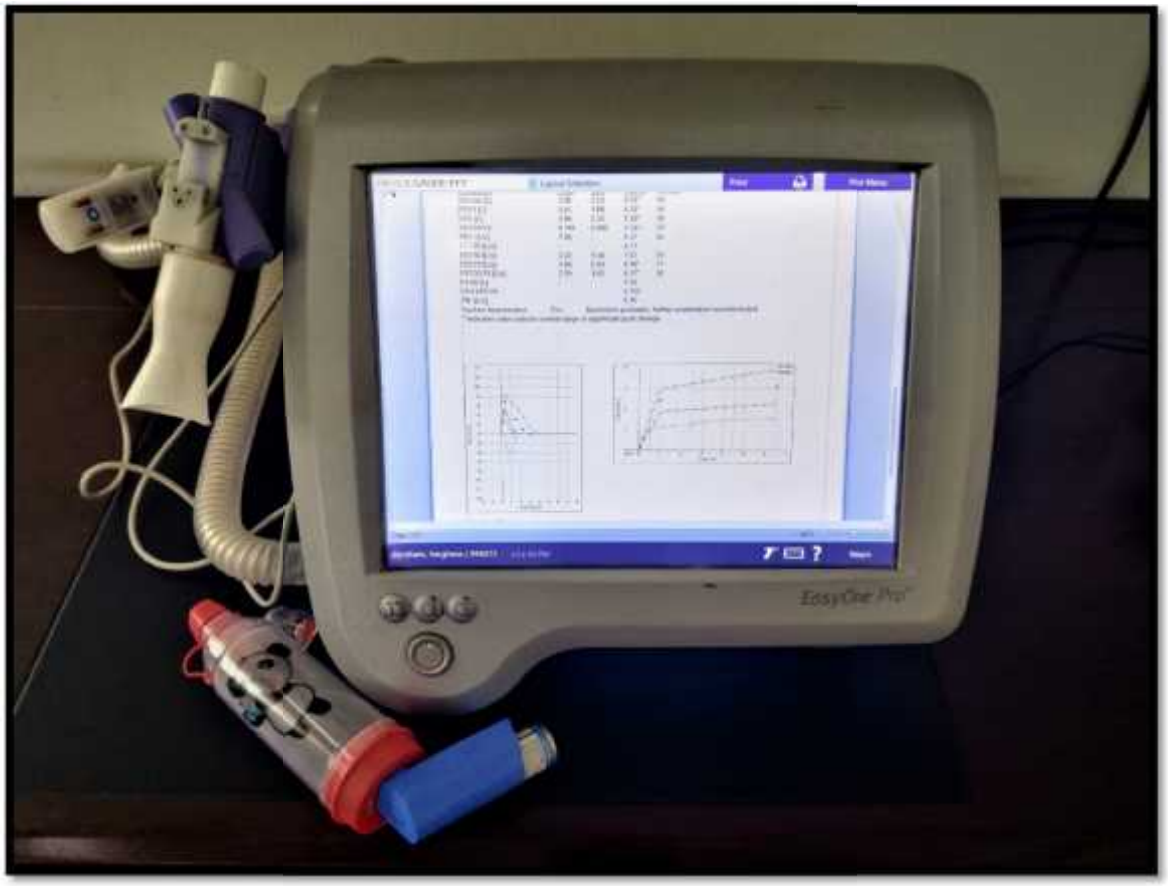
Duration of hospital stay -

Outcome -

ANNEXURE IV

PHOTOGRAPH

1. SPIROMETER



ANNEXURE V

KEY TO MASTER CHART

MDI	–	Metered Dose Inhaler
HbA1c	–	Glycated hemoglobin
FBS	–	Fasting Blood Sugar
RBS	–	Random Blood Sugar
PPBS	–	Post Prandial Blood Sugar
M	–	Male
F	–	Female
TLC	–	Total White blood cell counts
S.PCT	–	Serum Procalcitonin
FEV1	–	Forced Expiratory Volume in 1 second
FVC	–	Forced Vital Capacity
Sputum C/S	–	Sputum Culture and Sensitivity
ICU	–	Intensive Care Unit
IV	–	Intravenous
NIV	–	Noninvasive ventilation
BMI	–	Body Mass Index
SPO2	–	Arterial oxygen saturation
LTOT	–	Long term oxygen therapy