BONE HEALTH IN PATIENTS WITH CHRONIC OBSTRUCTIVE AIRWAY DISEASE- AN INDIAN PERSPECTIVE

(BOAD STUDY)

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE M.D. BRANCH I (GENERAL MEDICINE) EXAMINATION OF THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, APRIL 2015

CERTIFICATE

This is to certify that the dissertation titled **'Bone health in patients with chronic obstructive airway disease- an Indian perspective'** is the bonafide work of **Dr. Mohammad Sadiq. J,** in fulfillment of the rules and regulations for the **M.D., Branch I, General Medicine** Examination of **The Tamil Nadu Dr. M.G.R. University,** to be held in 2015.

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DECLARATION

I declare that this dissertation titled **'Bone health in patients with chronic obstructive airway disease- an Indian perspective'** has been conducted by me under the guidance and supervision of Dr. (Prof) **Samuel George Hansdak** (MD.). It is submitted as a part of the fulfillment of requirement of the award of degree of **M.D., Branch I, General Medicine,** for April 2015 examination to be held under **The Tamil Nadu Dr. M.G.R. University**. I have not submitted this thesis for the award of any degree or diploma from any other university.

Dr. Mohammad Sadiq. J

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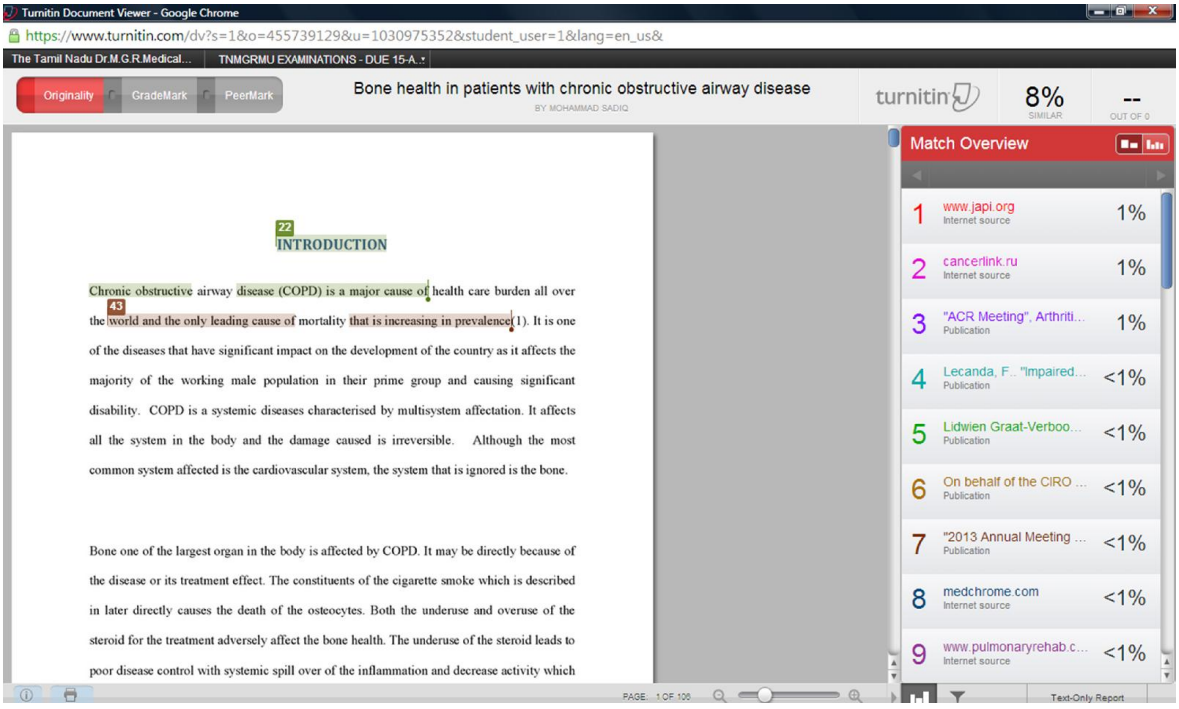
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INTRODUCTION
Chronic obstructive airway disease (COPD) is a major cause of health care burden all over the world and the only leading cause of mortality that is increasing in prevalence(1). It is one of the diseases that have significant impact on the development of the country as it affects the majority of the working male population in their prime group and causing significant disability. COPD is a systemic diseases characterised by multisystem affectation. It affects all the system in the body and the damage caused is irreversible. Although the most common system affected is the cardiovascular system, the system that is ignored is the bone.
Bone one of the largest organ in the body is affected by COPD. It may be directly because of the disease or its treatment effect. The constituents of the cigarette smoke which is described in later directly causes the death of the osteocytes. Both the underuse and overuse of the steroid for the treatment adversely affect the bone health. The underuse of the steroid leads to poor disease control with systemic spill over of the inflammation and decrease activity which
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INTRODUCTION

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The effect of COPD disease on the bone health is extensively studied in the developed nation. In India there was no study published during the start of this dissertation about the bone health in COPD. There were few studied the osteoporosis in patient with COPD but other aspects of the bone health was not assessed in these studies. What we have tried is to assess the COPD and the treatment as a whole affecting the bone health. This will give a picture of

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The Treasurer
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Vellore.

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Bone health in patients with chronic obstructive airway disease.
Dr. Mohammad Sadiq J, PG Registrar, General Medicine, Dr. Samuel George Hansdek, Medicine, Dr. Thomas V Paul, Dr. Nihal Thomas, Dr. Anjali Amit Bhatt, Endocrinology., Dr. Jayaprakash Muliyil, Dr. DJ Christopher, Pulmonary Medicine.

Ref: IRB Min. No. 7996 dated 08.09.2012

The Institutional Review Board at its meeting held on 08th September, 2012 vide IRB Min. No. ***7996*** accepted the project for *2 Year* at a total sanction of *Rs. 80, 000/- (Rupees Eighty Thousand Only)* A sum of Rs 40,000/- will be sanctioned for 12 months after receipt of the revised proposal, subsequent installment of 40,000/- each will be released at the end of the first year following the receipt of the progress report. Kindly arrange to transfer the sanctioned amount to a separate account to be operated by Drs. Mohammad Sadiq J, Samuel George Hansdek

Thank you.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MRAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
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CC: Dr. Mohammad Sadiq J, General Medicine, CMC.
Dr. Samuel George Hansdek, General Medicine, CMC.
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Dr. D. J. Christopher, Professor and Head, Dept. of Pulmonary Medicine,

Dr. Balamugesh Thangakunam, Professor, Dept. of Pulmonary Medicine

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CONTENTS

ABSTRACT

TITLE OF THE ABSTRACT : Bone health in patients with chronic obstructive airway disease- an Indian perspective

DEPARTEMENT : Department of General Medicine

NAME OF THE CANDIDATE : Dr Mohammad Sadiq. J

DEGREE AND SUBJECT : M.D., Branch I, General Medicine

NAME OF THE GUIDE : Dr. Samuel George Hansdak

OBJECTIVES:

To study the burden of osteoporosis, osteopenia and metabolic abnormality related to bone health in male patients with chronic obstructive airway disease in the age group between 40 to 70 years who are being followed up in Christian Medical College, Vellore.

METHODS:

Clinical methods:

This was a cross sectional study done over a period of two years at Christian Medical college Vellore. A detailed history and physical examination was done for all male patients with chronic obstructive pulmonary disease in the age group between 40 to 70 years, who were not on bone medications. Blood samples were collected for calcium, phosphorous, albumin,

alkaline phosphatase, creatinine, parathormone, 25-hydroxy vitamin D and testosterone. Lung functions test and six minute walk test were performed. Bone mineral density was assessed using DXA scan (dual energy x-ray absorptiometry).

Statistical methods:

Continuous variables were described using mean and standard deviation, if normally distributed. Interquartile range was used for skewed distribution. All categorical variables were summarized by using frequencies and percentages. Logistic regression model was constructed to assess the relationship between parameters showing positive correlation with osteoporosis in COPD (chronic obstructive pulmonary disease).

RESULTS:

A total of 67 patients were enrolled. The prevalence of osteoporosis among the male COPD patients was 61% (41/67) and an additional 33 %(22/67) had osteopenia. The prevalence of metabolic bone abnormalities in patients with COPD were: vitamin D deficiency in 69 %(46/67), hypocalcaemia in 4 %(3/67), raised alkaline phosphatase in 8% (6/67) and elevated parathormone in 31 %(21/67). The factors which showed a trend towards adverse bone health were: advanced age and low body mass index. Although these variables showed a positive trend towards osteoporosis in COPD patients, they did not achieve statistical significance.

CONCLUSION:

In this study the prevalence of osteoporosis and osteopenia among male COPD patients were 61% and 33% respectively, which is noted to be almost twice the prevalence as that of the general population.

KEYWORDS: Chronic obstructive air way disease; osteoporosis; osteopenia; vitamin D deficiency

INTRODUCTION

Chronic obstructive airway disease (COPD) is a major cause of health care burden all over the world and the only leading cause of mortality that is increasing in prevalence(1). It is one of the diseases that have significant impact on the development of the country as it affects the majority of the working male population in their prime group and causing significant disability. COPD is a systemic diseases characterised by multisystem affectation. It affects all the system in the body and the damage caused is irreversible. Although the most common system affected is the cardiovascular system, the system that is ignored is the bone.

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bone health was not assessed in these studies. What we have tried is to assess the COPD and the treatment as a whole affecting the bone health. This will give a picture of the disease with its treatment affecting the one of the largest tissue in the body. This help assessing the prevalence of adverse bone health in patient with COPD and the factors affecting it. This will help the clinician greatly to look for the adverse predictors and treat at the early stage to prevent the irreversible damage.

AIM

AIMS

To assess the prevalence of adverse bone health in patients with chronic obstructive pulmonary disease and associated factors that may contribute to it, among the patient seen in the outpatient department in a tertiary care centre in India.

OBJECTIVES

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1. To study the burden of osteoporosis and osteopenia in male patients in the age group between 40-70 years with chronic obstructive airway disease who are newly diagnosed or on follow up with Department of pulmonary medicine at Christian Medical College Hospital Vellore, Tamilnadu, India

2. To study the existing metabolic abnormality related to bone health in the same population.

3. To assess the determinants of adverse bone health in the population being studied

4. To make recommendations based on the findings.

REVIEW OF LITERATURE

Chronic obstructive pulmonary disease (COPD) is known to the mankind for the last 400 years. The first known description of COPD goes as back as 1679, when Theophile Bonet described 19 cases where the lung was turgid with air(2). Subsequently there were number of authors describe the disease in different terms based on the local risk factors and the clinical presentation. It was in the early 1960s after the two landmark meeting –"Ciba Guest symposium in 1959" and "American Thoracic Society 1962", defined the individual component of the disease. It was Dr William Briscoe, who defined the term COPD in the ASPEN Emphysema conference held in 1965. The spirometer was invented by Dr John Hutchinson as early as 1846. But till 1970 COPD was defined only in pathological terms in the post-partum studies. It was not until late 1990s that the consensus was developed to use the Spirometer to define COPD. It is a major breakthrough by the time patient develops the clinical signs of the disease the disease had already advanced to the state of irreversibility. It is killer disease with very high morbidity and mortality. The Global Initiative for Chronic Obstructive Lung Disease (GOLD), was a need of an hour initiative by the authority on world health- World Health Organisation (WHO) and National Heart, Lung, and Blood Institute (NHLBI) in 2001(2).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD, has defined COPD as a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients(1). The respiratory system affectation is characterised by both obstruction to the air flow in and out of the lung with diffusion restriction with certain phenotypes of COPD. The characteristic of the COPD is that the airflow obstruction is not reversible unlike in bronchial asthma where the airflow obstruction is reversible after the trial of the bronchodilator and it is usually a progressive disease. The

progressive nature is due to an abnormal inflammatory response of the lungs to noxious particles or gases.

The GOLD has classified into four stages (Table 1)(1). The classification is based on the patient with the symptoms or with risk factors of COPD with the measurement of Forced vital capacity and forced expiratory volume in one second (FEV_1) before and after the administration of the bronchodilator. The characteristics symptoms of COPD are dyspnoea, chronic cough and sputum production. The dyspnoea of COPD is characteristics which is progressive, persistent and worsens over time and exercise. The condition is characterised by frequent exacerbation. The risk factors for COPD are tobacco smoke, house hold smoke, dust and industrial pollution. There is also small group of patients who are congenitally predisposed to COPD like patients with α1-antitrypsin deficiency. It's the combination of these risk factors and abnormal inflammation that causes irreversible damage to the airway.

Table 1 GOLD staging of COPD. (FEV_1-Post dilator Forced expiratory volume at 1st minute, FVC- forced vital capacity)

GOLD Stage	**Spirometry**
I	FEV_1/FVC <0.7 and FEV_1 80% predicted
II	FEV_1/FVC <0.7 and 50% FEV_1 <80% predicted
III	FEV_1/FVC <0.7 and 30% FEV_1 <50% predicted
IV	FEV_1/FVC <0.7 and FEV_1 <30% predicted or FEV_1 <50% predicted with respiratory failure or Cor pulmonale

The salient feature of COPD is its significant extrapulmonary component which is very well emphasized in the current GOLD 2014 and it previous definition of COPD(1). More the 65% of the patient is characterised by atleast one extrapulmonary system affectation (3). The commonest extra-pulmonary system affected and which are extensively studies are the cardiovascular system characterised by systemic and pulmonary artery hypertension, congestive cardiac failure and arrhythmias. The other extra-pulmonary manifestations were increased risk of diabetes, metabolic syndrome and osteoporosis.

Global problem of COPD

COPD is a health problem with significant medical, social and financial impact on society. It has multiple adverse outcomes both to the patient, his family and the health system of the country. In patient's point of view, COPD causes physical disability, reduced quality and quantity of life. In relation to the health care system, it causes very high resource utilization, in terms of recurrent office visits, frequent hospital admissions due to acute exacerbations, and long term therapy (eg, long-term oxygen therapy, medication)(1).

COPD is underreporting grossly both in the developed and developing nation. It is because of the following

1. Symptoms of COPD which has frequent overlap with other pulmonary disease like pneumonia, asthma, etc.
2. Clinical signs appear late in the disease
3. Risk factors are common as smoking is common for number of pulmonary and extra pulmonary disease
4. Cost of diagnosis of the disease is high even in the developed nations

The prevalence of smoking is although high but it is underreported. The prevalence of COPD is even more under reported as compared to smoking. The prevalence of COPD worldwide is 15%-20% among smokers(4).The global estimate by WHO shows, 65 million people have moderate to severe chronic obstructive pulmonary disease (COPD). More than 5% of the death worldwide is attributed to COPD which is equivalent to 3 million, of which 90% occur in the low and middle income countries. These data are from the high income countries. Even in those countries, the predicted prevalence of the disease is low due to various factors as mentioned above. It ranks 4th in the disease causing mortality and ranks 12th-leading cause of disability-adjusted life years (DALYS, defined as the number of years lost due to ill-health, disability or early death") in 1990. It is expected to become 5th by 2020(5). Although COPD was considered more common in males but this demarcation in the gender is fading due to the increased exposure to tobacco smoke –both active and passive among women and increase in the indoor air pollution in developing nation like biomass fuel smokes.

Indian scenario of COPD

COPD is grossly underreported in India. The earlier studies which were conducted to assess the burden of COPD were small surveys, which varied in their methodology, tools and were difficult to interpret in resource poor setting. Based on these studies the prevalence rates vary from 2% to 22% in men and 1.2% to 19 % in women(6). These studies were based on the unvalidated questionnaires. Some studies also used house hold interviews with peak expiratory flow rate as the standard to make diagnosis of COPD. But the disease remained grossly underreported. The burden was steadily increasing warranting high quality nationwide analysis. It remained the challenge and it was the Indian Council of Medical Research (ICMR) took this

initiative and studied the epidemiology of this disease. The study was sponsored by the Indian study on Epidemiology of Asthma, Respiratory symptoms and chronic bronchitis (INSEARCH). This nationwide survey included 4-centres in the Phase I and 12 new centres in the Phase II study.

The results of the Phase I ICMR study were from Chandigarh, Delhi, Kanpur and Bangalore. This reported the prevalence rates of 5.0 and 3.2% respectively in men and women(7). An interesting comparison of this study with earlier studies shows the following

1. The prevalence rate of the disease (COPD) was almost the same i.e., overall 5% prevalence has been present in the earlier studies too.
2. India has doubled its population in the last three decades and hence the total burden of COPD has risen to 14.84 million in 2011 from earlier 6.45 million in 1971.

In India the disease is significantly more among Men and the Male to female ratio is distinct in Indian compared to the Western figures. This can be attributed to the cultural setting and male predominance of smoking(8). Although this ratio is slowly getting blurred due to non-cigarette particles from the pollution from different sectors contaminating the environment. And there is a significant contribution from the indoor smoke due to the biomass fuel use to which people in household are greatly exposed. This is particularly concern for the Women who are maximally exposed to this pollution. There is also a concern of passive smoking in the household contact for the Children and Women who may not be active smokers themselves(9). Although we know have the prevalence of COPD in India but the effect of the disease on the direct mortality still not yet clear. The limited data obtained from the Rural Household Survey and also Death Certification data provides an estimate of around 0.57million deaths were attributed to COPD in

1998. It was second most common cause of death after injuries among the non-communicable disease with an estimate of 0.57 million death in 1998(10). Similar but increasing figure were quoted in the NFHS I and II surveys. But we need more robust study to assess the COPD disease and its mortality effect. It's not only the mortality that affects the people but the significant disability it cause in terms of both health related and the non-health related ones. The financial aspects of this disease are alarming with increasing cost. The direct cost of care for COPD patient with stable disease is Rs 2440 as a direct per capita expenditure. And the indirect cost of care as one would expect is would the three times high as the direct cost. COPD hence not only kill people but also cripples them both medically and socially either directly or by its influence to affect the other system in the body.

Aetiology of COPD:

The important etiological factor attributed cigarette smoke. Both the particulate and non-particulate smoke has been attributed to the development of the disease. The most intruding aspect of the disease is the only 15% of the significant smokers develop COPD. And this percentage increases up to 50 % in the age group above 75 years old(11). There must an individual risk factor that would have predisposed to the disease either genetic or acquired. The other acquired risk factors were biomass fuel smoke, environmental toxic smoke from the industries and other particulate smoke. The pure individual genetic predisposition is seen only in very few cases like in patients with α-1 antitrypsin deficiency. Although there are multiple other genes were identified but their disease association has been the subject of controversy. Lower respiratory tract infection during childhood may increase the airway responsiveness to the offending agents(12).

Pathology of COPD:

COPD affect all the part of the lungs although the area most affected are the airway, the following area shows pathological changes in the autopsy study of the COPD lung in the decreasing order of frequency(13)

1. Both proximal and peripheral airway
2. Lung Parenchyma
3. Pulmonary micro and macro circulatory changes

These region shows infiltration lymphocytes which are predominantly CD8+ cytotoxic T-lymphocytes(14). The other players in the immunity circles are the macrophages and B-lymphocytes. These inflammatory cells induce secondary changes in the airway epithelium producing goblet cell hyperplasia, squamous metaplasia and increase in the size of the sub-mucosal glands(15). During the long run because of the repeated injury and healing, it produces fibrosis of the wall indicating the irreversible nature of the disease. The fibrosis is characteristically in the peri-bronchial in location.

Pathogenesis of COPD:

COPD is an inflammatory disease characterised chronic and progressive airway inflammation. The triggering event is not very clear but is assumed is to be due to cigarette smoking in the genetically predisposed individual. The sequences of events in the COPD lung that lead to disease are as follows(16)

1. Presentation of antigen by the naïve dendritic cells and macrophages –the antigen is in question is multiple and the most common is the particulate smoke in the cigarette smokers

2. The antigen is presented to the naïve T-cell in the lymph node
3. The T-cell response characterised by the infiltration of the airway epithelium with cytotoxic CD4+ lymphocytes and macrophages.

These cause infiltration of inflammatory cells and necrosis of the airway epithelium caused due to the proteolytic enzyme secreted by these cells (Figure 1). The abnormal inflammatory response is attributed to the genetic polymorphism in the gene expression activating these enzymes (**Table 2**)(17).

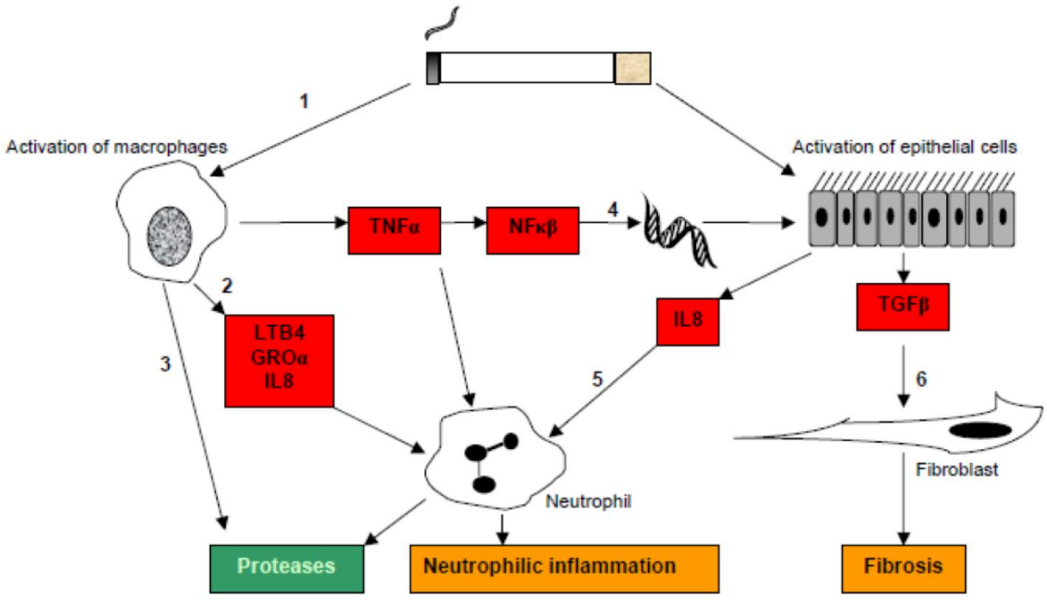

Figure 1 Pathogenesis of COPD (TNF-Tumor necrosis factor, NF-Nuclear factor, IL-Interleukin, LTB-Leukotriene B and TGF-transforming growth factor)

Table 2: Gene involved in the pathogenesis of COPD (Matrix metalloproteinase, TIMP-Tissue inhibitor of MMP, SERPINA-gene coding for antitrypsin)

Gene/Protein	Polymorphism ID	Gene ID
MMP9	CR994492	4318
MMP1	rs1799750	4312
MMP12		4321
TIMP2	rs2277698	7077
SERPINA3	rs4934	12

COPD is a systemic disease:

GOLD has defined COPD as a systemic disease with significant extrapulmonary effects. It took many years for this understanding of COPD as a systemic disease. The commonest cause of death and increased morbidity is most often due to it systemic effect like increase in the cardiovascular disease and metabolic abnormalities in patient with COPD(18). The problem arises in differentiating this systemic effect of COPD from the shared risk factor between the systemic disease and COPD (Figure **2**). A patient with risk factor of smoking could have increased risk of atherosclerotic cardiovascular disease and COPD because of the shared risk factor between the two. This confusion should not jeopardize the clinical care of these patients.

This difficulty is defining co-morbidity from systemic effect is not only present in COPD in fact present in almost all disease. The definition of co-morbidities and systemic cannot be strictly applied to COPD as there is multiple shared risk factors. Indeed it was right defined by the GOLD as COPD is the systemic disease rather than isolated pulmonary disease(1).

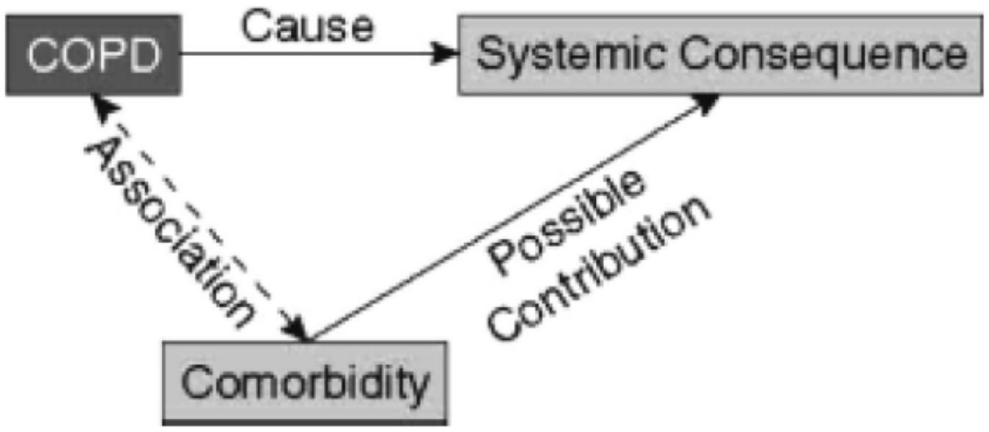

Figure 2 : Diagram showing the relationship between systemic effect and co-morbidities

The evidence for the increase in co-morbidities in patient with COPD was shown by Mapel et al who showed that an average of 3.7 co-morbidities were present in COPD patient compared to the controls who had an average of 1.8(19). The co-morbidities that were present in this cohort of patient were heart failure, metabolic syndrome, sarcopenia, osteoporosis and depression. Similar result was shown by Crisafulli et al that patient enrolled for pulmonary rehabilitation(20). They found that there were atleast one co-morbidity was present in 62% of the patient.

The commonest co-morbidities that was found to be significant in multiple studies were listed below

1. Dyslipidaemia
2. Diabetes mellitus,
3. Systemic Hypertension, ,
4. Chronic heart failure
5. Coronary artery disease, and
6. Osteoporosis

These above six contribute to the total of 86% of the co-morbidities detected in various studies. In a landmark trial ECLIPSE which studied the co-morbidities in COPD patient found the following results(21)

1. The three groups were compared –Smoker with proven diagnosis of COPD, smoker without COPD and non-smoker
2. The prevalence of the co-morbidities were 38%, 23% and 16% respectively in the above groups with $p<0.001$
3. Air flow limitation did not influence the prevalence of these co-morbidites

The presence of co-morbidities has adverse impact on the disease with respect to mortality and also morbidity. It is very difficult to differentiate between the co-morbidities and the systemic effects. As noted in another trial 67% of the COPD patients have atleast one systemic organ dysfunction(3).

What cause this systemic dysfunction? There is no direct answer to this question. But there have been some postulates. The two important which is widely accepted are

1. Systemic spill theory
2. Compartment model

Systemic spill theory states that there is spill of the cytokines from the chronic inflammation in the airway epithelium(22). The evidence to support this theory comes from the studies indicating the increase in surfactant D protein which is produced only from type II pneumocytes is increased in the systemic circulation in patient with COPD. The surfactant D protein helps in the innate defence system in killing micro-organism. But this is not consistent across other studies(22). The compartment model states that there is two or more compartment of which one must definitely be pulmonary causing COPD and there is the distant organ affected due to the shared risk factor between COPD and other disease. The distant organ affected as mentioned earlier were cardiovascular system, metabolic abnormalities and bone(23). This thesis focuses on bone health in patients with COPD and factor contributing the adverse bone health. The main determinant of the bone health is adequate mineral and remodelling. The deficiency of the mineral leads to number of condition of which an important the important one is osteomalacia and increased resorption lead to the porous bone named with a condition called Osteoporosis.

This thesis focuses on different aspects of the bone health in patients with COPD.

OSTEOPOROSIS

A systemic skeletal disease, osteoporosis is characterized by a decreased in the bone mineral density (BMD) as well as deterioration of its microarchitecture. It thus results in an increase in the fragility of bones and hence an increased susceptibility to fractures.

Dual energy absorptiometry (DXA) scan is the current gold standard to diagnose osteoporosis(24). With this technique a definite bone mineral density (BMD) is acquired by measuring the amount of mineral in the scanned area of bone in grams divided by the measured bone surface in square centimetres

The BMD score of patients is then expressed as T score, which is calculated by measuring the standard deviations by which the patient's BMD varies from the mean BMD of a young control population. The International Society for Clinical Densitometry advices measuring BMD both at the lumbar spine and the hip, WHO advocates the measurement of the same at the hip alone(25). Of all the measured locations, the lowest T-score is used for the diagnosis of osteoporosis. Therefore osteoporosis according to the WHO is defined based on the basis of T-score(Table 3)(24).

Table 3: World Health Organisation (WHO) classification of osteoporosis based on the T-score

Normal	**T-score ≥ -1**
Osteopenia	-1 > T-score > -2.5
Osteoporosis	T-score ≤ -2.5
Established osteoporosis	T-score ≤ -2,5 and fragility fracture(s)

For a whole body DXA-scan the cut-off values for osteoporosis and osteopenia must be adjusted according to Boyanov in order to obtain a good sensitivity to specificity ratio(Table 4)(26).

Table 4 Classification of whole body bone mineral density according to Boyanov (26)

Normal	**T-score > -0.90**
Osteopenia	-0.90 < T-score < -2.35
Osteoporosis	T-score < -2.35

Of the different aspect of the bone health, only the BMD is measured by DXA scan, however, as mentioned before, Osteoporosis is characterized by not only a decrease in the mineral density of bones but also by a deterioration its microarchitecture. It results in fragility fractures. A DXA-scan measures only the mineral density of bones, but no way it can assess the deteriorated microarchitecture within.

However an indirect way of assessing the same is a vertebral fracture in the past without a high energy trauma. According to Genant et al, by virtue of a morphometric method, vertebral deformities can be assessed on X-rays of the spine(27). Anterior, medial and posterior heights

of each vertebra are measured, following which comparisons are made amongst them and also to the heights of the vertebrae above and beneath that vertebra (Table 5)(28).

Table 5 Morphometric method of vertebral fracture analysis

Grading	Radiological appearance
Grade 1	20-25% reduction in anterior, middle and/or posterior height and 10-20% reduction of the projected vertebral area
Grade 2	25-40% reduction in height and 20-40% reduction of the projected vertebral area
Grade 3	≥40% reduction in height

Fractures can also be classified according to their shape (Figure 3)(28).-

- Wedge -reduction in anterior height
- Biconcave -reduction in middle height
- Crush -reduction in posterior height

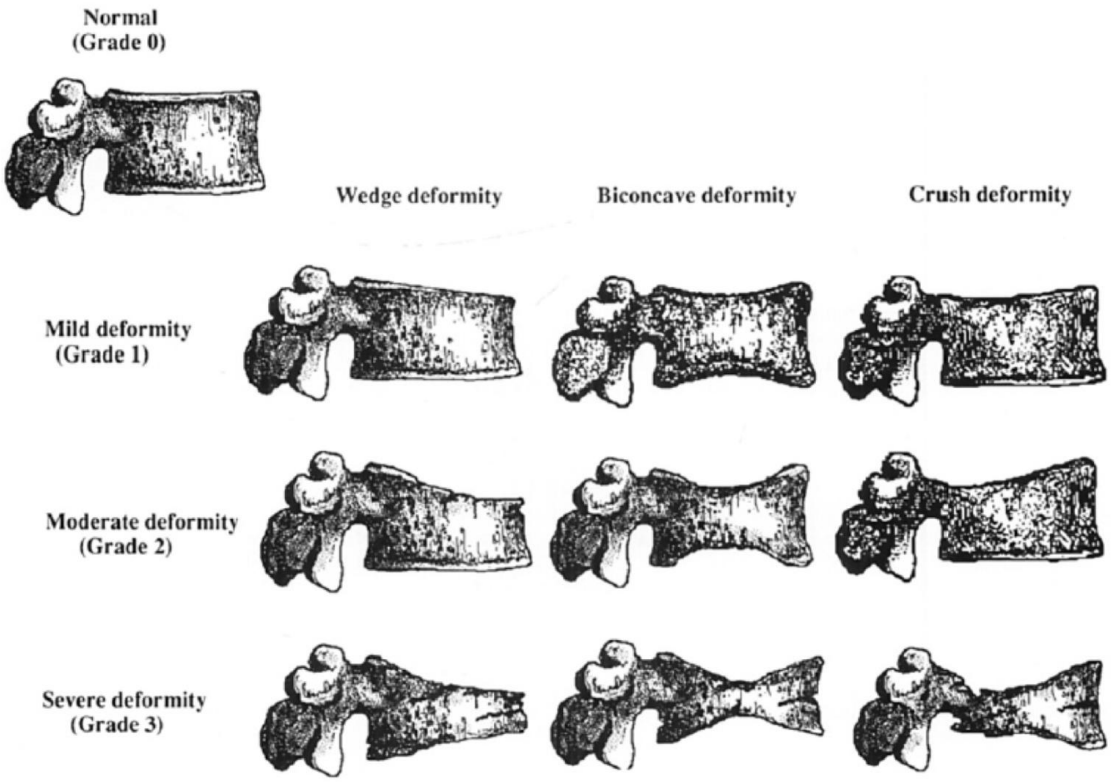

Figure 3: Visual grading of the vertebral deformity and morphometric analysis(28)

In a study conducted by Cummings et al patients with a normal bone mineral density as determined by DXA-scan did have vertebral fractures, thus supporting the fact that osteoporosis can be due to a deterioration in the bone microarchitecture even in the presence of a normal bone mineral density(29).

Epidemiology and impact of osteoporosis:

According to the World Health Organisation (WHO) a population of more than 75 million people in Europe, Japan and the USA is affected with osteoporosis(24). In fact, the lifetime risk for osteoporotic fractures has been estimated to be near about 40%, which is similar to that for coronary heart disease. To make matter worse, osteoporosis also causes loss of height, back pain

and decreased quality of life. Moreover, a fracture increases the mortality e.g. the risk of death is increased over ten-fold in the first seven days following a fracture(30).

Aetiology of osteoporosis

Multiple aetiological factors have been identified. Risk factors for osteoporosis as well as osteoporotic fractures include increased

- Advanced age,
- Lower body mass index,
- smoking,
- Greater than three units of alcohol per day,
- Previous fracture before 50 years of age,
- Parent with a fracture,
- Immobility,
- Systemic glucocorticoid usage and
- Systemic connective tissue disorder.

Pathology of osteoporosis

Bone remodelling is a dynamic process. It is initiated on the surface of the bone. Lining cells on the bone surface respond to both local as well as systemic cytokines and hormones. Remodelling of a bone is the result of the coordinated activity of osteoclastic bone resorption and osteoblastic bone formation. Differentiation of osteoclasts is stimulated in interaction with

osteoblastic cells. This interaction involves binding of the receptor activator of nuclear factor kappa β (RANK) on osteoclasts to its ligand (RANKL) expressed by the osteoblast cells (Figure 4)(31).

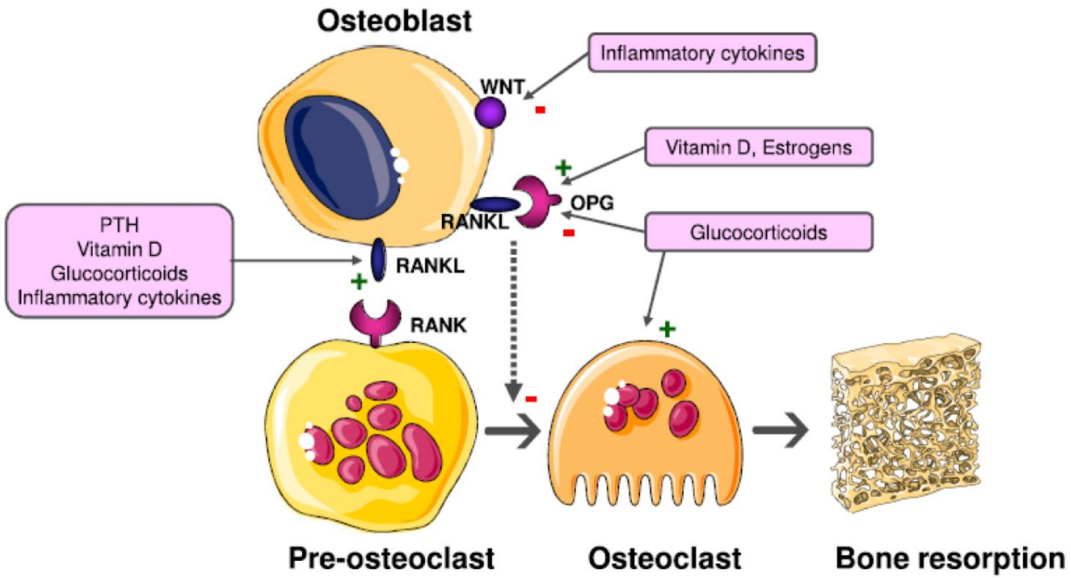

Figure 4: Important steps in osteoporosis in COPD (RANK- receptor activator of nuclear factor kappa, RANKL-RANK ligand, OPD-Osteoprotegerin, PTH-Parathormone)(31).

This binding of RANK to RANKL promotes both the differentiation as well as activity of osteoclasts. The tumor necrosis factor Receptor-Associated Factor (TRAF) adaptor proteins play an important role in the initial event of RANK induced signal transduction pathway. Most likely TRAF proteins act by transmitting the RANK induced signal to downstream targets (which includes nuclear factor kappa β). Osteoprotegerin (OPG) is secreted by osteoblasts; it acts as a natural decoy receptor. OPG binds to RANKL and thus inhibits the binding of RANK to RANKL. Thus OPG prevents bone loss in case of postmenopausal osteoporosis. The Wnt signalling pathway (Wnt stands for Wingless-related integration site) also plays an important

role in the formation of bones by activating osteoblasts and inhibiting the osteoclast for bone resorption. This happens through series of activation of cascade proteins and transcription factors (**Figure 5**)(32).

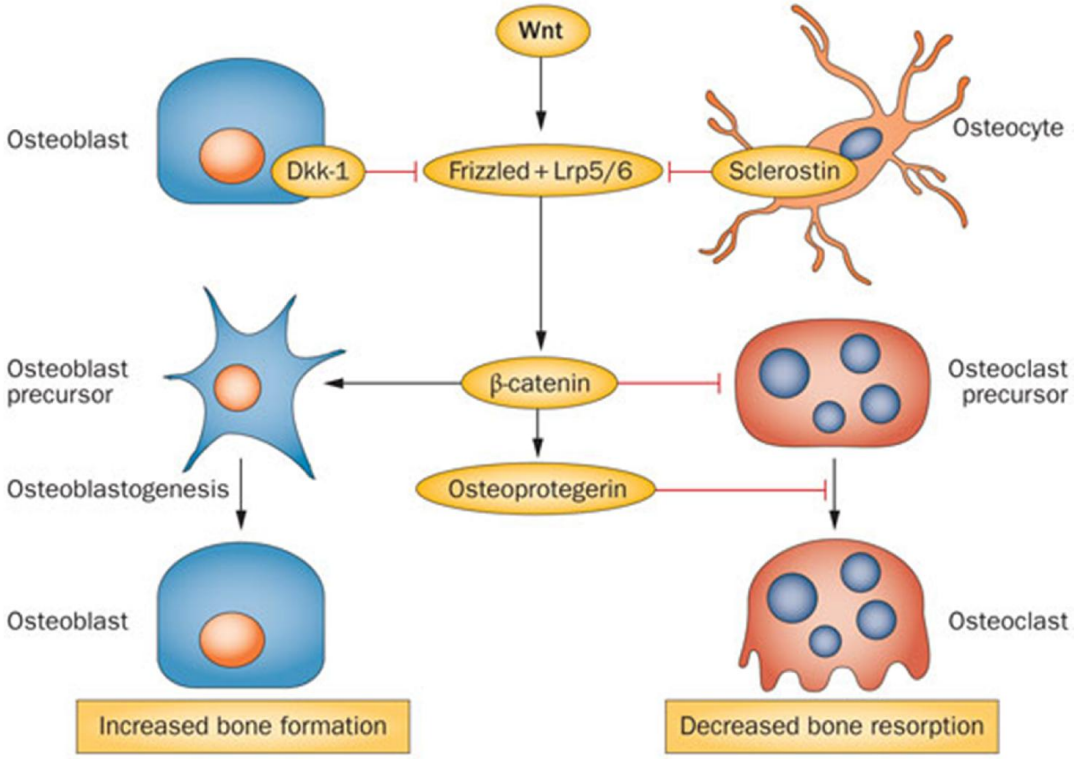

Figure 5 Wnt signalling increases bone formation and decreases resorption. It suppresses osteoporosis by osteoprotegerin and β catenin mediated pathways and increases bone formation through Dkk-1 and sclerostin mediated pathway. (LRP, LDL receptor related protein co-receptor, Dkk-1, Dickkopf-related protein 1)(32)**.**

Wherever there is increased bone remodelling, there is an increase in the risk of fracture and this is due to multiple factors- the primary reason being a decrease in the stiffness of the bones. This is reduced because a bone which was once more densely mineralized gets replaced with less densely mineralised younger bone. Bone remodelling also increases the fragility of bone and

this happens because of impairment in the maturation of collagen due to an alteration in the cross linking between the adjacent collagen fibrils. Finally, the sites which undergo resorption remain temporarily naked, and thus predispose the bone to microdamage as a result of stress concentrators. Factors which increase bone remodelling include both calcium as well as vitamin D deficiency by virtue of secondary hyperparathyroidism.

Osteoporosis and other chronic diseases:

There are several chronic diseases involving a single or multiple systems that lead to secondary osteoporosis in the long run. In fact the prevalence of secondary osteoporosis has been found to be significantly high in those with inflammatory bowel disease, sarcoidosis and also COPD. Systemic inflammation is the common link amongst all these disease conditions. Indeed, it proves that chronic IBD cause production of cytokines which in turn stimulate bone turnover. This leads to an increase in bone fragility and hence an increased risk of fracture. Indeed, Bon and his colleagues found a correlation between the C-telopeptides of type I collagen (which is a marker of bone resorption) and interleukine-4 as well as tumor necrosis factor α in COPD patients which was significant(33). Moreover, they also found a significant correlation between the N-terminal procollagen propeptide (again a marker of bone formation) and both IL- 4 as well as TNF-α. Another link between these diseases and osteoporosis could be physical inactivity, which in turn leads to a low BMD. Also certain risk factors for osteoporosis and some chronic diseases are similar e.g. smoking. However, pathogenesis of osteoporosis in these chronic diseases is very complicated & not fully understood yet.

OSTEOPOROSIS AND COPD:

GLOBAL:

Osteoporosis is highly prevalent among patients with COPD. In fact it is estimated to be a whopping 2 to 5 times higher in those with COPD in comparison to healthy subjects(34). Study done by Graat et al showed that in developed nations the prevalence of osteoporosis in patients with COPD is somewhere in between 4% and 59%(35). Differences in the study population, diagnostics methods as well as difference in the severity of the underlying disease in the studied population lead to this highly wide range. In the past increased prevalence of osteoporosis in COPD patients was solely attributed to the use of corticosteroids. However, it was also seen that corticosteroid naive COPD patients also had a high prevalence of osteoporosis among them, and hence it suggests a more complex mechanism underneath(36). Measures of a low body composition and measures of disease severity are the correlates of osteoporosis in COPD. Prevalence of vertebral compression fracture in those with COPD has been explored by multiple studies and it was reported to vary from 24% to 63%. The prevalence of hip fracture in COPD patients has not been studied in details yet. However a study done by Walsh et al has shown that there is an increase in the prevalence of hip fracture in those with miscellaneous lung conditions out of which around 52% were diagnosed with COPD(37).

However most of these studies used only DXA in order to assess osteoporosis. Morover, most of them were cross sectional. Given the fact that fractures of the hip pose an increased operative risk in those with COPD as compared to healthy subject, the prevention of osteoporotic as well as vertebral fractures becomes all the more important in COPD patients(38). To add to all worries, a vertebral fracture might lead to a decrease in the forced vital capacity(39). Moreover, treating these fractures is itself very complicated with a lot of risks involved such as venous

thromboembolism and also peri-operative complication. Therefore, an early and efficient treatment of osteoporosis should be considered. This treatment should not only consist of pharmacological therapy but also lifestyle advises (for example weight baring physical exercise, cessation of smoking and the use of dairy products). The former should consist of bisphosphonates and calcium with/without vitamin D. However, to date, it is still not well known whether and also to what extend physicians prescribe any bone medications to COPD patients with osteoporosis.

Risk factors for osteoporosis in those with COPD:

Both COPD and osteoporosis are chronic conditions. Osteoporosis has been found to occur in a significant number of patients with COPD. However, it is not very clear whether the increase in the prevalence of osteoporosis in COPD patients as compared to healthy subjects is due to a common underlying pathophysiological mechanism or a consequence of multiple shared risk factors. Chronic diseases are also characterized by end organ damage. Such damage may be the result of continuous interaction of common (both modifiable and non-modifiable) as well as intermediate risk factors(40). COPD and osteoporosis have multiple common risk factors (**Table 6**). A detailed discussion of some of these risk factors can be found below-

Table 6 Risk factors for COPD and Osteoporosis

Common risk factors		Intermediate risk factors
Modifiable	Non-modifiable	
Nutrition	Genetic	Visceral fat
Physical inactivity	Gender	Repair
smoking	Aging	Vitamin D deficiency
		Systemic inflammation

Nutrition and body composition:

A common risk factor for osteoporosis identified in general population is low BMI(41). As a consequence of low BMI there is reduced mechanical loading on the bones which in turn leads to a loss in the bone mass; as studied by Cavanagh et al and this was clearly evident among the astronauts(42). Indeed, in multiple studies a low BMI was found to be a common factor among COPD patients with osteoporosis.

Research done both earlier as well as recently, strengthened the importance of body composition in the disease manifestation and prognosis of COPD. A lower than normal body weight has been found to be an independent risk predictor of mortality in those with COPD.

Reduced muscle mass, which is assessed by measuring fat free mass, is an even better predictor of mortality as compared to BMI in such patients. In addition, a low muscle mass has also been found to be associated with a poor health status in patients with COPD. Previous studies have reported a significantly high prevalence of fat free mass as well as low body weight in COPD patients; this ranges from 20% in clinically stable outpatients to a whopping 41% in those requiring pulmonary rehabilitation. In fact, one of the characteristic findings of cachexia is a low fat free mass.

Besides malnutrition, cachexia is caused by an imbalance in protein breakdown and synthesis. A commonly used marker of protein breakdown is pseudouridine (PSU)(43). Protein breakdown can be easily assessed using PSU as it offer the advantage of not requiring any dietary limitations; also it is a suitable marker because once it is produced, it is neither metabolized further nor reused by the body. Indeed, in paediatric patients receiving growth hormone therapy, a significant negative correlation was shown between changes in PSU concentrations in urine and ornithine concentrations in plasma (which is a traditional marker of anabolism in tissues). The fact that protein imbalance can cause cachexia was shown by an increased pseudouridine in patients with a low fat free mass (FFM), low fat free mass index (FFMI), and also impaired skeletal muscle function(34). Protein breakdown in these patients will not only cause a reduction in the muscle mass, but it will also induce a loss in bone tissue. Bolton and colleagues found in their study that those with a low FFMI had an increased PSU levels and also a lower BMD(44). This study also correlated a low FFMI to interleukin-6 (IL-6), thus indicating that systemic inflammation could possibly be the link between a low body composition and osteoporosis in patients with COPD. However, studies done by other researchers such as

Broekhuizen et al did not come across a significant correlation between body composition and systemic inflammation(45).

Increased mechanical loading could be the reason as to why an overweight or obese COPD patient is protected from osteoporosis. Mechanical loading results in bone formation probably by stimulation of osteocytes that act as mechanosensors and thus respond to motion of the fluid in the lacunae and the canaliculi within a bone. This in turn leads to a positive balance within the bone remodelling cycle; and thus an increased BMD(46).

Another factor that could be protective in overweight or obese patients could be leptin. A part of the cytokine family, leptin is produced primarily in the adipocytes and it circulates in the blood. Its blood levels are directly corresponds to the amount of body fat i.e. those with a higher adipose reserve have increased blood levels of leptin(47). Leptin functions by inhibiting appetite by virtue of its action on the receptors located in the hypothalamus. In addition, leptin promotes formation of bones by increasing the proliferation and also the differentiation of osteoblasts. It is believed that this effect of leptin could be enhanced in obese patients with COPD since circulating leptin levels were found to be higher in female COPD patients in comparison to healthy subjects matched for age and BMI(48).

However a negative effect on bone metabolism has also been found. Therefore, it could be that leptin has a biphasic effect on bone: a lower serum levels promote increasing bone formation but suppresses bone formation at higher serum levels. In patients with COPD a significant positive link was established between BMD and serum leptin levels, however, such an effect was not independent of body mass(47).

Physical inactivity:

COPD patients have been found to be physically less active in comparison to healthy subjects. These patients showed lower standing time, walking time and also significantly less movement intensity during walking(49). They also had higher lying time and sitting time. It was also found that approximately 30 to 50% COPD patients walked less than a mere 30 min every day, which is, in fact, the recommended minimum amount of regular physical exercise that is necessary to develop physical fitness. As expected the physical inactivity would be more in GOLD stage IV COPD than with stage I patients.

The precise mechanism by which physical inactivity leads to osteoporosis is not very clear yet. Nevertheless, studies in both human and animal have proved that disuse, especially if its long term, leads to decrease in the BMD, disorder in the architecture of bones, a reduction in the bone mechanical properties; the consequence of all these is an increase in the incidence of bone fracture. Moreover, physical inactivity results in sarcopenia which may play a role in bone loss(50). In addition, weakness of muscles of the lower limbs exerts a significantly powerful influence on the incidence of hip fractures due to its effect on the risk of falls. Physical exercise, especially those involving weight bearing activity were found to have a positive effect on the BMD. Indeed, a decreased BMD was experienced by astronauts in weight-bearing bones. Further research is required to establish the dose-response relationships between bone strength and exercise and also the duration as well as the form of exercise.

Smoking and COPD:

There is an increased risk of osteoporosis with smoking in the general population. Indeed, a 2-4 fold increase in odds ratio for osteoporotic fractures was found in smokers compared to healthy non-smokers in multiple case control studies(51). However, it is not yet clear how smoking induces osteoporosis. Smokers usually have a lower body weight as compared to their non-smoking peers; this reduced BMI could possibly be the reason behind the high prevalence of osteoporosis among smokers. Menopause occurs at an earlier age among women who smoke as compared to non-smoking healthy female subjects; the age at onset of menopause being a very strong predictor for osteoporosis. Also there seems to be an adverse effect of cigarette smoke on those hormones which are involved in the process of regulation of bone metabolism; example includes alkaline phosphatase and parathormone. However the underlying mechanism is not fully known but whatever the mechanism could be, smoking seems to have a dose effect which is clearly evident by virtue of the fact that the effect on bone mineral density in found in both male and female subjects of higher age having a long term history of smoking(52). Additionally, in young adults, smoking was found to exert a significant effect on bone mass in studies which included only the heavy smokers in the analysis. Also we know that the effect of cigarette smoking on the bone status is associated mainly with the duration and amount of smoking in the elderly population(51). It might also be that smoking causes a decrease in bone mass by bringing up an alteration in the blood levels of hormones produced from the adrenal cortex.

A lower level of 25-hydroxyvitamin D has been found to exist in smokers in comparison with non-smokers in several studies; however the precise mechanism of this association is not yet. Enhanced metabolism of the metabolites of vitamin D in the liver as a result of induction of

hepatic enzymes by virtue of smoking has been suggested as a possible mechanism for a lower vitamin D levels in smokers as mentioned above(52). Impaired calcium absorption is another significant factor which enhances bone loss in individuals who smoke. The absorption of calcium was found to be lower in smokers in comparison to subjects who did not smoke after adjustment was made for age, gender, intake of calcium supplements as well as dietary calcium and vitamin D intake, especially in those individuals who had smoked >20 cigarettes/day(47). Finally, smoking exerts a significantly more deleterious effect on the bone mass in men when compared to women; also men have greater tobacco intake than women (Figure 6). However, on the other hand, in women, the reduced influence of cigarette smoking on the bone mass may be due to the interference of either oral contraceptive metabolism or because of oestrogen replacement. In addition very little data is available on the possible association that smoking, duration, length of time after cessation, type of tobacco and fracture risk.

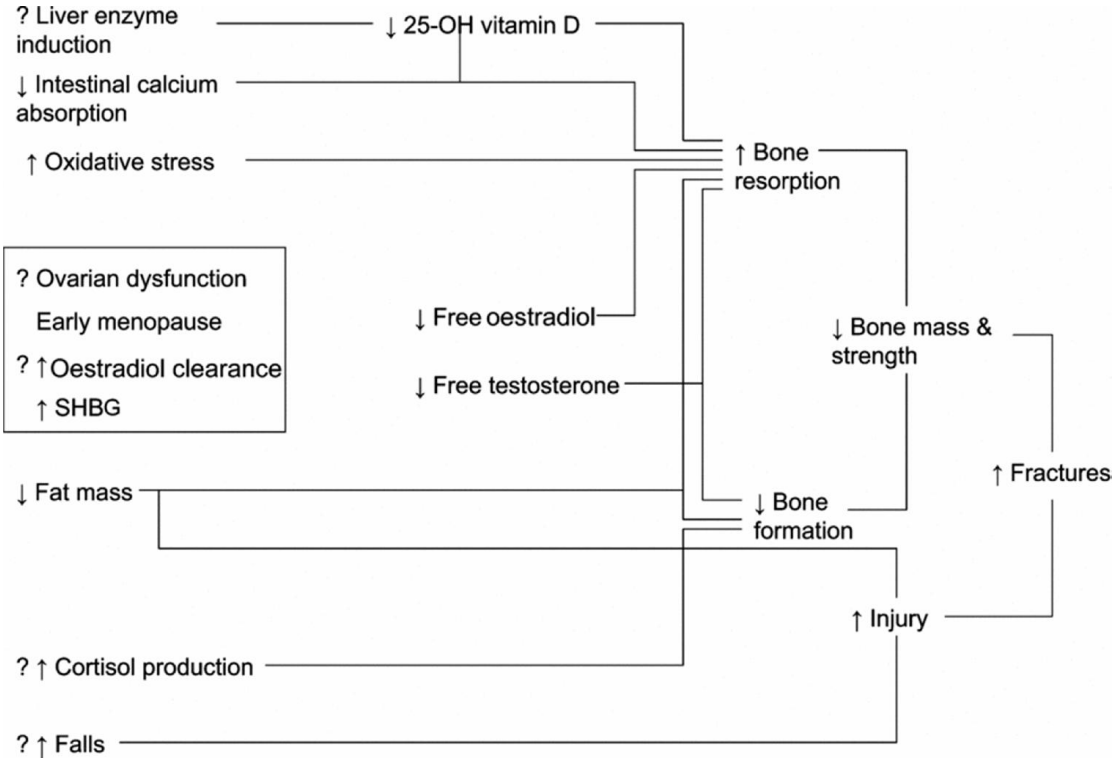

Figure 6 Effect of smoking on various aspects of the bone health (SHBG- sex hormone binding globulin)

The exact molecular mechanism underlying this effect of smoking on bone mass has not been studied extensively yet. In vitro studies have demonstrated a decrease in the proliferation and impairment in the synthesis of collagen in osteoblast-like cells which were exposed to high concentrations of nicotine as well as the non-nicotine constituents of found in cigarette smoke. One of the studies used a bone graft revascularization rabbit model to show this effect(53). The authors implanted a cancellous bone graft into the distal femur of the experimental specimen and demonstrated impaired vascularization of the implant in presence of elevated levels of nicotine in the system. Other authors have been successful in demonstration of osteoblasts death as a result of direct harmful and toxic effects of smoking(51).

Systemic inflammation:

The prevalence of osteoporosis is high in various systemic inflammatory conditions, common examples being inflammatory bowel disease, (rheumatoid) arthritis and sarcoidosis(54). This serves as an indirect indicator that the development of osteoporosis maybe caused or accelerated by the presence of systemic inflammation. As a matter of fact, numerous studies have conclusively proven that even with a small increase in the level of any systemic inflammation, there can be substantial precipitation of bone loss in an individual(55). Indeed, it can emerge as a strong and independent risk factor for occurrence of osteoporotic fractures.

Chronic inflammatory conditions activate the immune system which in turn leads to the synthesis of molecules which exert a negative effect on the process of bone homeostasis. A significant feature that is associated with inflammatory bone loss is enhanced osteoclastogenesis and hence increased bone resorption; however in inflammatory diseases the formation of bones is blunted rather than being enhanced. In the process of inflammatory bone loss, there is an increase in the recruitment of precursors of osteoclasts from within the bone marrow and thus osteoclastogenesis is enhanced. Once the precursor cells are recruited, the osteoclasts undergo differentiation from their precursor cells. This process is mediated by prostaglandin and cytokines.

The mechanism underlying suppression of bone formation is in chronic inflammatory diseases is not clear yet. However, with the little data that we have, it has been shown that proteins such as Dickopf 1 and sclerosin are induced by tumor necrosis factor α (TNF- α)(56). These proteins

are potent inhibitors of the Wnt pathway and thus they can blunt bone formation leading to symptoms of osteoporosis and its sequelae. In COPD patients there is evidence of existence of a chronic low grade inflammation in the system. We should also note that this systemic inflammation is very heterogeneous, which is evident due to different levels of increased acute phase proteins, cytokines and other circulating cells that were identified in numerous studies.

A cross sectional study which including 409 patients with COPD and 231 healthy subjects without COPD, showed an independent rise of C-reactive protein (CRP) as well as monocyte chemo attractant protein (MCP)-4 in male patients with COPD. Several chemo-attractants and cytokines were found to be increased in patients with COPD in a study conducted among 48 COPD patients who were compared to a set of 48 matched controls(57). A few of these biomarkers were IL-15, interferon gamma, TNF-α and IL-17. As discussed earlier, in inflammatory diseases, the expression of RANKL is exaggerated by cytokines. In the Bergen cohort study, in COPD patients the level of OPG was found to be dysregulated.

A significantly lower level of OPG was found in COPD patients when compared to healthy subjects without COPD; surprisingly a higher plasma OPG level was associated with a low FEV1 and also COPD exacerbations in previous years. Bon and colleagues studied 40 COPD patients who required lung transplantation; they discovered that there exists a direct correlation between markers of systemic inflammation i.e. IL-4 and TNF-α and that of bone metabolism that include N-terminal procollagen propeptide (PINP) and C-telopeptides of type I collagen (CTx)(33). However unfortunately, in the cohort study by Bergen, the bone status of the

subjects was not assessed and in the study by Bon et al OPG levels weren't measured(46). Therefore, the possible correlation between inflammation, the bone status and the OPG/RANK/RANKL system in those with COPD is not proven yet.

The Wnt-signaling pathway is influenced by inflammatory cytokines as shown in those with artrithis. Recently, a decreased Wnt/β-catenin signaling was shown to be involved in destruction of the lung parenchyma and it also leads to an impairment of the repair mechanisms in emphysema. Wnt-signaling plays a significant role in formation of bones by activating osteoblasts(32). Thus, the role of this Wnt-pathway on osteoporosis in COPD patients warrants further investigation.

Vitamin D deficiency and osteoporosis in COPD:

A varied prevalence of vitamin D deficiency was found among patients with COPD. Numerous studies have been undertaken and this prevalence was found to be somewhere in between 32 to 51%(58). Vitamin D was found to be an independent risk factor for osteoporosis in number of prospective studies. Moreover, an increase in the PTH levels by virtue of secondary hyperparathyroidism in turn increased the odds ratio for osteoporosis. Additionally, apart from the effects of vitamin D on bone, non-calcemic effects of the same are described(59). Beside the kidneys, other tissues where 1-α-hydroxylase can be found are the skin, bone and also in immune cells. In these extra renal tissues the expression of 1-α-hydroxylase is regulated by immune signals (instead of mediators of calcium & bone homeostasis). High concentration of local 1,25-hydroxyvitamin D have autocrine as well as paracrine functions. Moreover, 1,25-

hydroxyvitamin D also controls genes that are involved in the regulation of cellular differentiation, proliferation and apoptosis.

Finally, 1,25-hydroxyvitamin D is also an immune modulator and therefore it stimulates the immune response to an infection. Indeed, vitamin D deficiency has been found to be associated in many diseases like malignancy, type I diabetes, rheumatoid arthritis, the metabolic syndrome, congestive heart failure and tuberculosis. Examples of non-calcemic effects of vitamin D deficiency in COPD patients are inflammation and muscular dysfunction. In summary, vitamin D deficiency has both calcemic and non-calcemic effects(59).

Exogenous hormonal factors:

It is a well-known fact that the regular use of corticosteroids significantly increased the risk of osteoporosis. This is a result of uncoupling of bone formation as well as resorption. Inhaled corticosteroids were also found to have a dose related adrenal suppression which is a very well known risk factor for development of osteoporosis. However, studies done to assess the effects of inhaled corticosteroids on bone have several conflicting results. Gerald and colleagues conducted a meta-analysis and showed that inhaled corticosteroids did have a toxic effect on the markers of bone turnover as well as BMD in patients with COPD or asthma(60). As shown in TOwards A Revolution of COPD Health Study (TORCH) significant effect of inhaled corticosteroids was seen as compared to the placebo on the metabolism of bones in COPD patients who have been followed up for atleast 3 years now(61).

Its been found that there is an increased prevalence of apoptosis of osteocytes and a fewer no of osteoblasts in patients diagnosed to have oral corticosteroid induced secondary osteoporosis in comparison to healthy subjects. This apoptosis of the osteocytes is associated with a decrease in

the skeletal angiogenesis, bone strength and bone interstitial fluid possibly causing a loss of bone strength in those with corticosteroid-induced osteoporosis which usually occurs before the loss of BMD. Indeed, COPD patients who were also using oral corticosteroids were at a higher risk of fracture(55). Despite the fact that the use of oral corticosteroids in COPD patients is not recommended, they are often prescribed in stable COPD.

INDIAN

There was only one study that was published prior to the onset of this (BOAD study) which examined the problem of bone loss in COPD patients. Bhattacharya et al studied numerous patients with COPD commercially available ultrasound bone densitometer (HOLOGIC SAHARA)(62). Frequency of both osteoporosis and osteopenia was found to be high (73%). There was one more study which was published during the process of this dissertation which showed similar results(63).

TAMILNADU

There was no published data to our knowledge regarding prevalence of osteoporosis in COPD patient in Tamilnadu

JUSTIFICATION

At the outset, as mentioned above at the beginning of this study there was only study published regarding the prevalence of Osteoporosis in India. There was certain limitation of this study(62)

1. Use of a technique which was no yet standardised. A meta-analysis of 25 studies that evaluated the sensitivity and specificity of calcaneal ultrasound for identifying patients with DXA T-scores ≤-2.5 concluded that currently used ultrasound cutoff thresholds do

not have sufficiently high sensitivity or specificity to definitively exclude or confirm DXA-diagnosed osteoporosis

2. Another major limitation to using quantitative ultrasound as a screening tool is that the criteria for diagnosing osteoporosis and recommending treatment based upon ultrasound are not yet well established

3. Ultrasound cannot reliably be used to follow patients who are treated for osteoporosis because of limited precision and a slow rate of change of bone mass at peripheral sites.

There was another study that was published from Karnataka by Hattiholi et al(63), assessing the prevalence of osteoporosis. This study showed around 80% of patient with COPD has osteoporosis and Osteopenia. This was did not assess the other aspect of bone health like daily calcium intake and sunlight exposure. It also did not take into account the andropause induced decreased bone mass. And it was published after the completion of the present dissertation

In view of these issues, this study was designed to provide data to help answer the queries raised above. Lab parameters were also checked to look for any possible correlations and to rule our confounders. The result of this study will help to follow up the patient and treat early to prevent osteoporotic fracture.

MATERIALS AND METHODS

MATERIALS AND METHODS

Study type:

It's an Analytical study done at Christian Medical College, Vellore, Tamilnadu.

STUDY DESIGN:

It was designed as an observational study with a cross-sectional design.

It involved observation of patient with Chronic Obstructive Pulmonary disease

Data were obtained and recorded.

Analysis of the obtained date was done subsequently

There was no therapeutic intervention planned as part of this study.

SETTING:

The study was conducted among the patients visiting the outpatient services of Department of Pulmonary Medicine, Christian Medical College Hospital, Vellore.

The details of recruitment of patients is presented in the flow chart below

It was conducted under the auspices of the

- Departments of General Medicine,
- Department of Endocrinology, Diabetes and Metabolism,
- Department of Pulmonary Medicine and
- Department of Clinical Biochemistry, Christian Medical College.

DURATION OF THE STUDY:

The study was conducted between September 2012 and June 2014.

The recruitment phase spanned a period from December 2012 to March 2014.

INCLUSION CRITERIA

- Male patient diagnosed to have COPD as per GOLD COPD criteria
    - Female patient not included to reduce the confounding effect of post-menopausal osteoporosis.
- Age 40-70 years old
    - This age group is chosen to maintain uniformity in age in study population as COPD as well as osteoporosis become more common as age advances
- Patient residing in Tamil Nadu
    - This criterion is applied to maintain uniformity in ethnicity and dietary pattern in study population
- No localized lesion on chest X-ray
    - To avoid pulmonary function test abnormalities caused by respiratory diseases other than COPD

EXCLUSION CRITERIA

- Patient on diuretics
    - As these patients are likely to have electrolyte imbalance. Also patients on diuretics may be unwell to complete the evaluation.
- Patients requiring Oxygen supplementation
    - As these patients will unwell to complete the evaluation.
- Renal failure
    - It will be difficult to interpret the result because of pre-existing metabolic bone disease
- Liver failure (For similar reasons as mentioned above)
- Patient on bone medication like calcium, Vitamin D and Bisphosphonates
    - As these drugs will modify the bone health
- Mentally disabled persons
    - Who will be unable to give a valid consent
- History or being treated for cancer

- As some cancer will influence bone health

- Patient diagnosed or being treated for HIV infection

As the diseases per se and the medication used to treat alters the bone health

SAMPLE SIZE

The sample size was calculated using prevalence data from previous studies conducted in and round the country and outside the country(62,63). The calculation was based on the assumption that similar prevalence would be present in our study.

As referenced previously the prevalence of low bone mineral density (osteoporosis and osteopenia) widely varies between the populations studied. With the prevalence of Low BMD of 73-80% as shown among patient with COPD by Bhattacharyya et al was taken for the sample size calculation(62).

The following calculation (P=Prevalence of low bone density as 80%) yielded the sample size of 64 for this study.

$$n = \frac{4*p*q}{d^2}$$

Where:

n is the sample size,

q= 100-p= 20

d= precision= $\pm$ 10%

PATIENT RECRUITMENT:

Consecutive patients visiting pulmonary medicine outpatient services of Christian Medical College Hospital, Vellore were screened and patient with or newly diagnosed to have COPD as per the GOLD criteria were enrolled in to the study if they meet the inclusion and exclusion criteria

All included enrolled patients were provided with the study details in the form of patient information sheet in the language they understand and was explained by the Principal investigator after which a written consent was obtained (Annexure.)

The following information were collected with the tools as given below

CLINICAL ASSESSMENT AND ANTHROPOMETRY

The qualitative variables like history of COPD and other diseases and their treatment and that associated with the various facets of lifestyle including, nutritional, physical activity were ascertained using a standardized questionnaire. A detailed history regarding current and past medications for management of COPD (including oral and inhaled steroids, their dose and duration) as well as pre-existing co-morbidities (eg. Diabetes, hypertension, dyslipidemia) was obtained.

Weight – Weight was measured by an electronic weighing machine by asking the patient to stand steady for 10 seconds on the platform.

Height – Height was measured from the highest point of vertex to the ground level by standardized measuring tape when the patient is standing on an even ground with his occiput, buttocks and heels touching the wall.

Waist circumference - As per the expert committee y WHO, Waist circumference was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest.

Waist-Hip ration - Waist-Hip ration was calculated by dividing waist circumference by measurement around the widest portion of the buttocks.

Dietary calcium intake- Dietary calcium intake was calculated by the 24 hours dietary recalled method and sunlight exposure was calculated form duration the patients are exposed to the sunlight when the shadow formed due to sunlight is larger than the real image.

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LUNG FUNCTION TEST

Spirometry - Spirometry was performed by Respiratory Therapist by Jaeger spirometer as per American Thoracic Society Guidelines. Patients were classified according to the severity as per the GOLD criteria (Table 1).

Six minute walk test was performed to calculate the distance covered (in meters) in 6 minutes as per the American Thoracic Society Guidelines

Furthermore BODE Index was calculated for all the patients to assess severity. The BODE Index is a composite marker of disease taking into consideration the systemic nature of COPD (**Table 7**).

Table 7 BODE severity index (FEV1% predicted defined as a percentage of the forced expiratory lung volume in one second; 6MWD = six minute walking distance; MMRC = modified medical research council dyspnea scale; BMI = body mass index)

Parameter/Points	0	1	2	3
BMI	>21	≤21	—	—
FEV_1 (% predicted)	≥65%	50–64%	36–49%	≤35%
MMRC score	0-1	2	3	4
6 MWT(meters)	≥350	250–349	150–249	≤149

LABORATORY ASSESSMENT

Fasting blood samples will be collected for the assessment of the following analyses (reference normal ranges in our laboratory shown parenthetically):

- Serum calcium (8.3 to 10.4 mg/dL),
- Serum phosphorus (2.5 to 4.6 mg/dL),
- Serum alkaline phosphatase (40 to 125 U/L),
- Serum albumin (3.5 to 5.0 g/dL),
- Serum creatinine (0.5 to 1.4 mg/dL),
- Serum 25-hydroxyvitamin D [25(OH)D] (normal 30 ng/mL or greater),
- Serum intact parathyroid hormone (iPTH) (8 to 50 pg/mL),
- Serum total testosterone (300 to 1,030 ng/dL), and
- Serum Cortisol measured at 8 am.

The biochemical variables were measured by microanalyzer manufactured by Hitachi model 911. The intra-assay and interassay coefficients of variation of the variables being studied from these machines were 1% to 5%. A radioimmunoassay manufactured by DiaSorin, Stillwater, was used to estimate of 25-OH vitamin D levels. The intra-assay coefficient of variation was 5.5% and 9.3% at a 25(OH)D level of 15.6 ng/mL and 52.5 ng/mL. iPTH respectively. The serum testosterone was measured by chemiluminescence by Immulite 2000 analyzer.

Assessment of BMD was perfomred by using the Hologic machine (QDR 4500; Hologic) at the lumbar spine (L1 to L4), forearm, femoral head and the femoral neck. The reference population consisted of normal white subjects used by the manufacturer's database. The precision was 2%. The World Health Organization criteria for osteoporosis was used for analysis.

STATISTICAL ANALYSIS:

The data collected was entered in Excel spread sheet (annexure). Continuous variables were described using means and standard deviations, if normally distributed. For variables with skewed distributions medians with interquartile ranges were used to summarize the distribution. All categorical variables were summarized by using frequencies and percentages. Logistic regression model was constructed in order to assess the relationship between parameters showing positive trend with osteoporosis in COPD. All statistical analyses were done using SPSS version 11 software (SPSS, Inc., Chicago, Illinois).

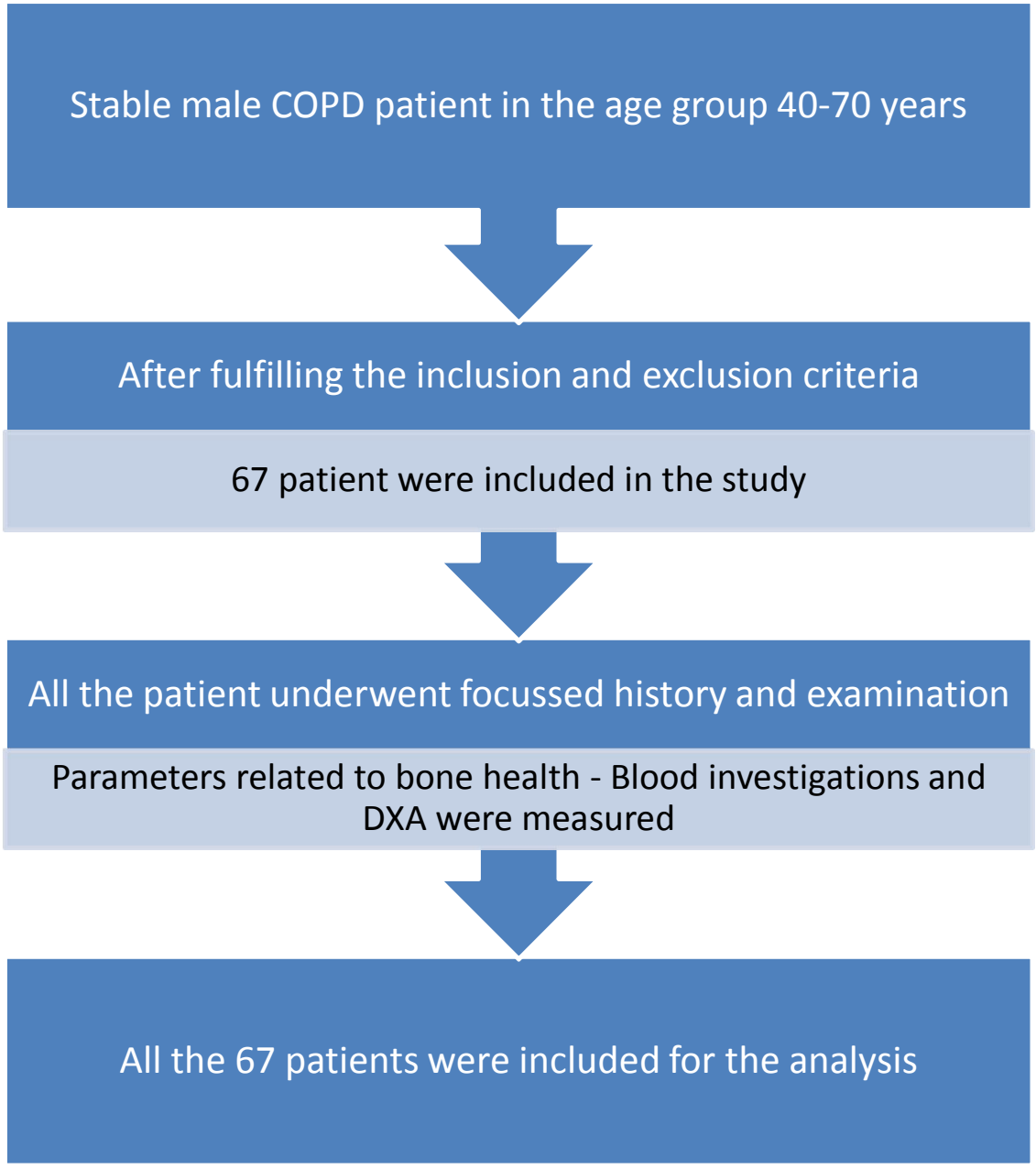
FUNDING:

The funding for the study was provided by the institutional review board for this specific purpose and also by the individual funds of the Department of Endocrinology, Diabetes and Metabolism.

INSTITUTIONAL REVIEW BOARD APPROVAL AND ETHICAL CONSIDERATIONS:

The study was presented to the Intuitional Review Board and was approved by it and by the ethics committee of Christian Medical College, Vellore. [IRB Min No: 7996 dated 08.09.2012]

STROBE STATEMENT



RESULTS

BASE LINE CHARACTERISTICS:

The baseline characteristics of the 67 patient after enrolled into the study after full filling the inclusion and exclusion criteria are as follows (Table 8).

Table 8 Baseline characteristics of the study population

Parameter	Mean ±SD
1. Age (years)	60±6 years
2. Duration of COPD (Months)	Median- 60 (Range- 6-354)
3. Smoking status (number)	
a. Never smoked	7
b. Current smoker	7
c. Ex-smoker	53
4. Smoking pack-years	Median – 30 (Range- 5-120)
5. FEV1 (% of predicted)	42.25±18
6. FVC	61.37±17
7. FEV1/FVC	67.67 ± 17
8. GOLD staging (number)	
a. Stage I	1
b. Stage II	18
c. Stage III	25
d. Stage IV	23
9. 6 MWT distance (meters)	347.97
10. BODE index	
11. Oral steroid use	
a. Dose (mg)	10mg – 40 mg(Range)
b. Duration (days)	Median- 7 (Range5-120)
12. History of Diabetes(number)	15
13. History of Hypertension (number)	10
14. Dyslipidemia	15
15. Sunlight exposure(<30 minutes)	9
16. Dietary calcium intake(<1000mg/day)	26

Age category:

The patients recruited were between the ages 40 to 70 years with the median of 60±6 years. The lowest age was 50 years and the highest was 70 years. The age distribution for each decade is shown in the (**Figure 7**)

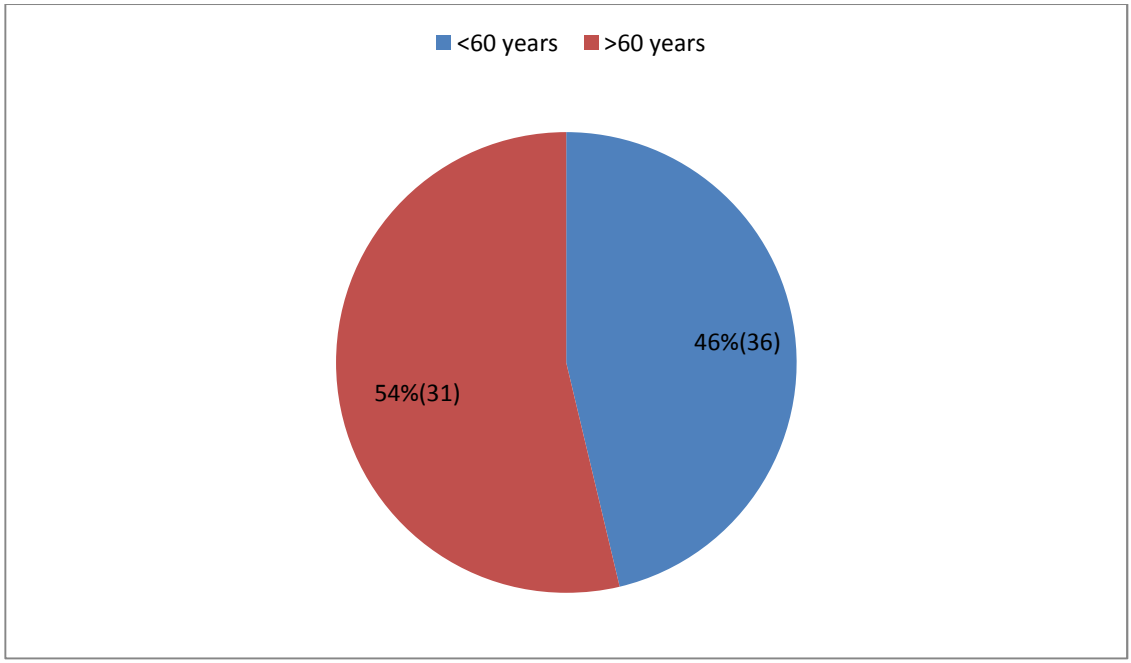


Figure 7 Age distribution of the patients included in the study.

When divided into two categories for above and below 60 years, there were almost equal numbers of patient above and below 60 years. This division was done to understand the risk of osteoporosis as the age advances. The prevalence was more in advanced age group as compared to the younger age group. This is because of the number of hormonal and non-hormonal mechanism that comes into play with advancing age.

Duration of COPD

The mean duration of COPD of the patient enrolled in the study is 62 months and the median is 48 months and the range is between 2months to 360 months. The patients were divided in to four categories based on the duration for further analysis (**Figure 8**).

- Category 1- less than 12 months , n=10 patients
- Category 2- 12 months to 60 months, n=35 patients
- Category 3- 60 months to 120 months, n=22 patients
- Category 4-more than 120 months, n=4 patients

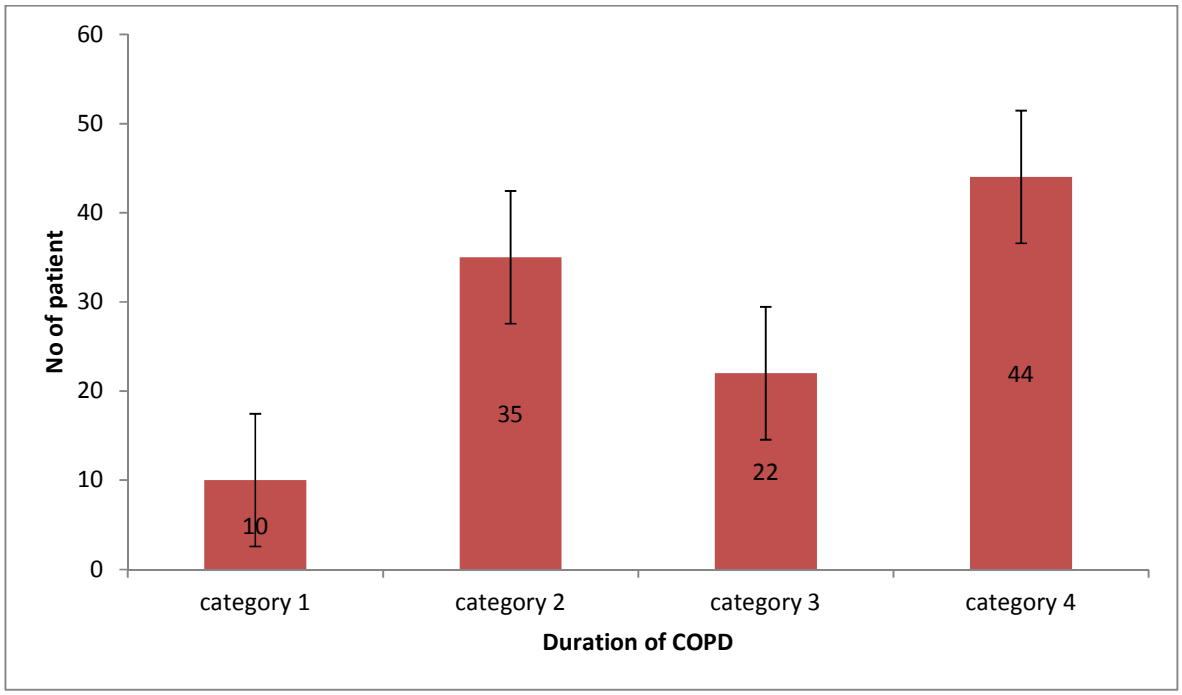


Figure 8 Error bar plot showing the duration of COPD of the study population. (Category 1, 2, 3 and 4 implies duration disease < 12 months, 12 to 60 months, 60 to 120 months and more than 120 months respectively)

GOLD stage of COPD

The majority of the patients were distributed equally in the Stage II, III and IV. There was only one patient in stage I disease (**Figure 9**).

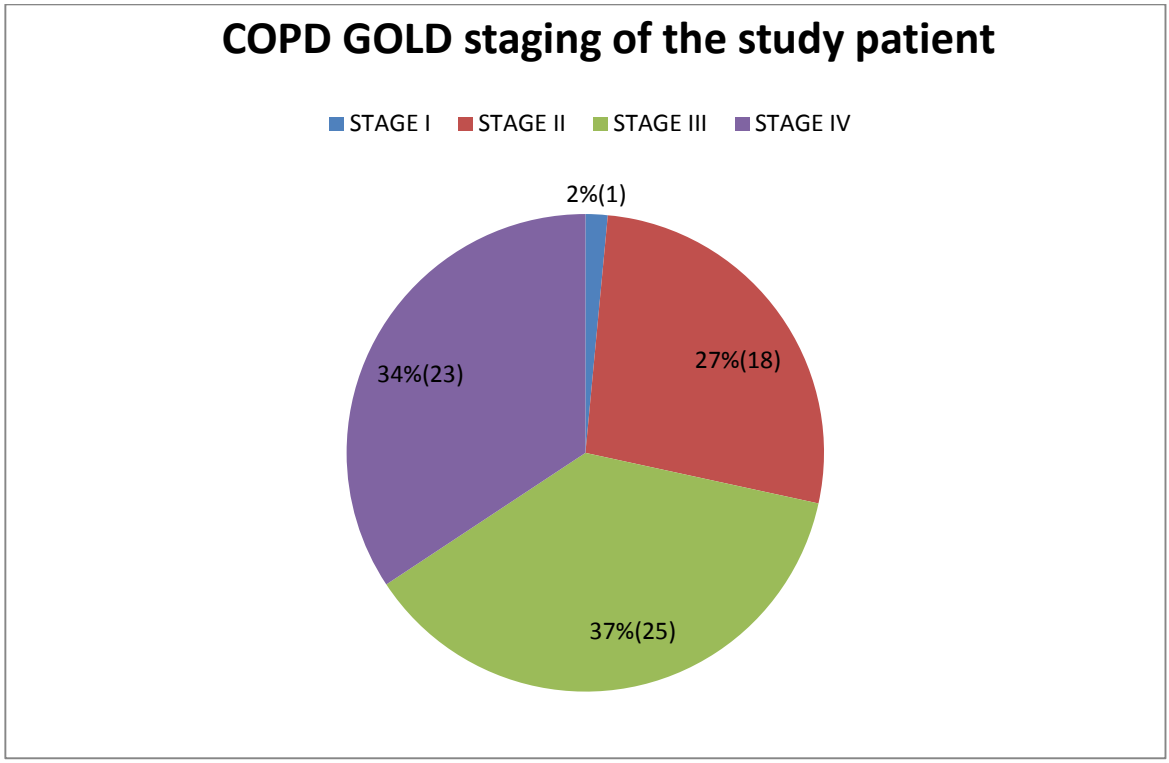


Figure 9 GOLD COPD staging of the patient. There were equal numbers of patients in all the stages except in stage I which represent the mild disease

COPD is classified into four stages from Stage I to IV (Table 1). Stage I disease is being mild and stage IV being severe. This division is based on the spirometry value and not based on the patient symptoms or day to day activities except in the stage IV disease. Hence this system of division of patient purely on the basis of spirometry value was criticized. This problem can be overcome by using the BODE severity index.

SEVERITY OF PULMONARY FUNCTION TEST:

All patients underwent spirometry testing if there was no lung function testing done in the last one year. The spirometry values for FEV1 and FEV1/FVC were studies and was plotted

FEV1 trend

The trend across the FEV1 values were studied and plotted. Patient in COPD have progressively declining FEV1 as the disease advances

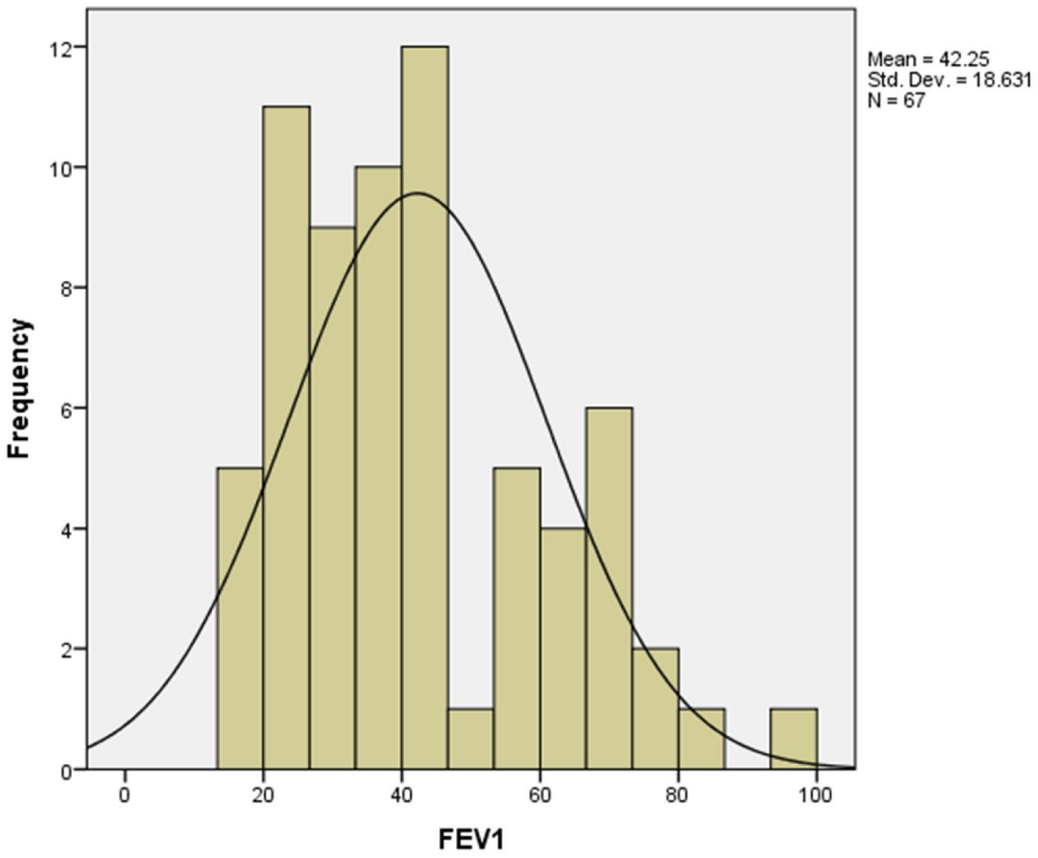


Figure 10 FEV1 Histogram showing the trends across the entire patient (FEV_1-Post dilator Forced expiratory volume at 1st minute, FVC- forced vital capacity).

The mean FEV1 of the study population was 42.25% with standard deviation of 18.63 (**Figure 10**). In the above histogram the FEV1 values very tend to cluster in the 30% to 60 % range indicating moderate severity of the disease population in this study population.

FEV1/FVC ratio:

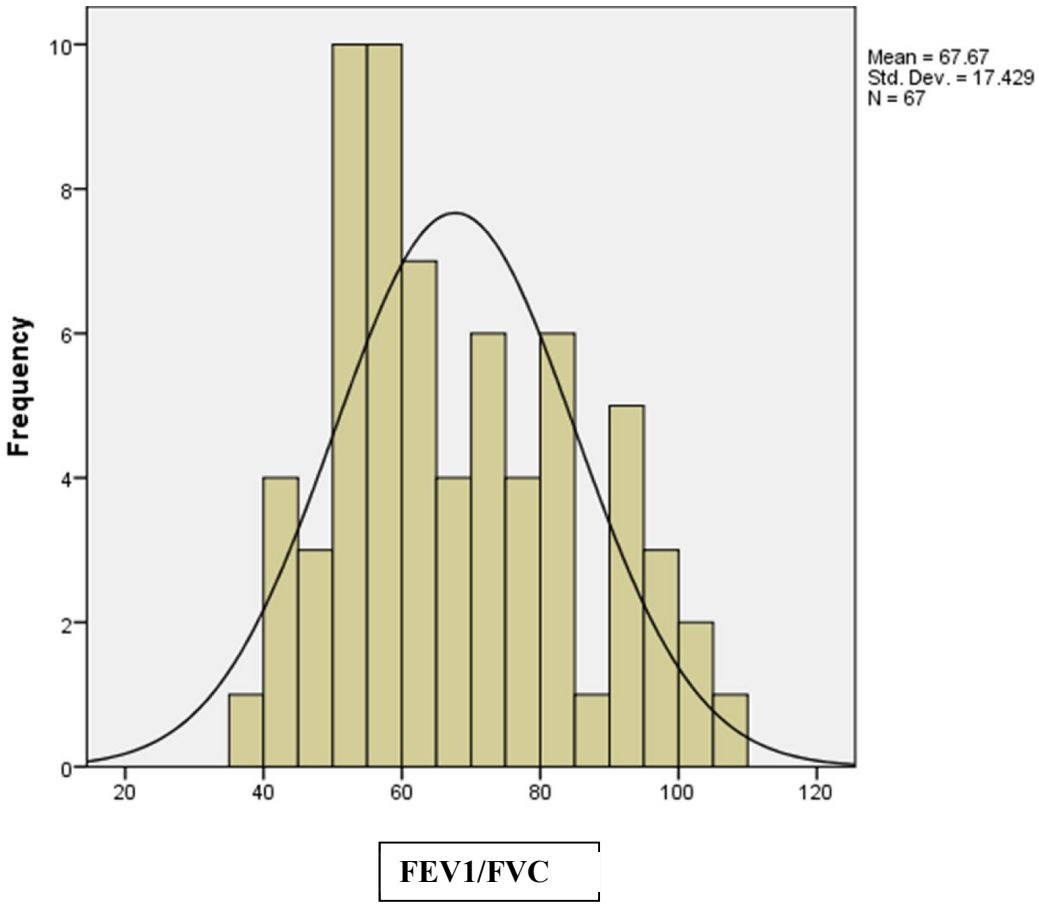


Figure 11: FEV1/FVC histogram showing the trends across the entire patient (FEV_1-Post dilator Forced expiratory volume at 1st minute, FVC- forced vital capacity).

The FEV1/FVC ratio showed the similar trend as compared to FEV1. There was one patient in stage I disease. The mean FEV1/FVC ratio was 67.7 with standard deviation of 17.4 (Figure 11). Although spirometry is used for diagnosis of COPD, but in Stage I disease where the

FEV1/FVC ratio is near normal. Hence stage I disease is mainly diagnosed clinically in patients who has risk factor for the disease with clinical signs for the same.

Six minute walk test

All patients also underwent six minute walk test. The six minute walk test is the quantitative method for assessing the severity of COPD with respect to restriction to the day today activities. The more the distance walked with normal saturation the less severe is the disease. The vice versa is true. And also used for follow up.

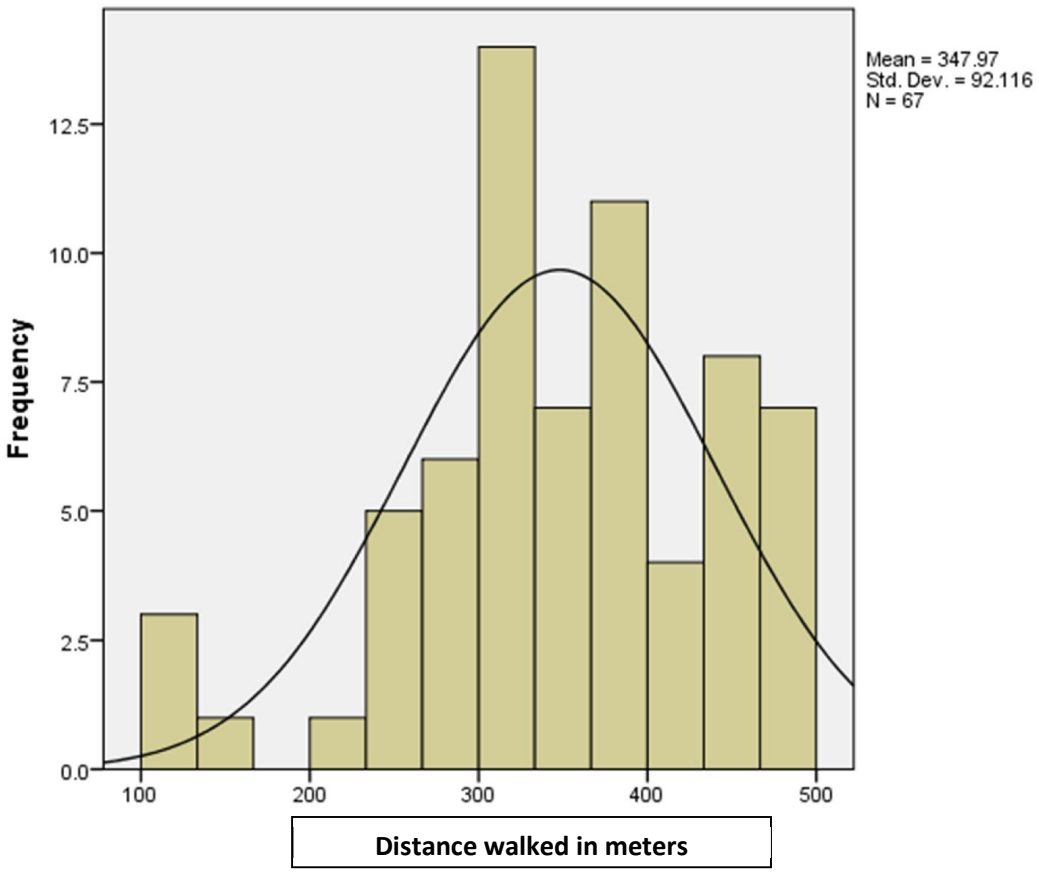


Figure 12: The histogram shows the trend among the study patient in the six minute walk test

The mean and median distance walked is shown in the histogram (Figure 12). Most of the patient covered only moderate walking distance. This is the quantitative way of estimating the disease activity restricting the patient activities of the daily living.

Modified medical research council (MMRC) scale:

Each and every patient in this study underwent qualitative and quantitative dyspnoea assessment. The dyspnoea assessment that we used was the MMRC scale which has been previously validated.

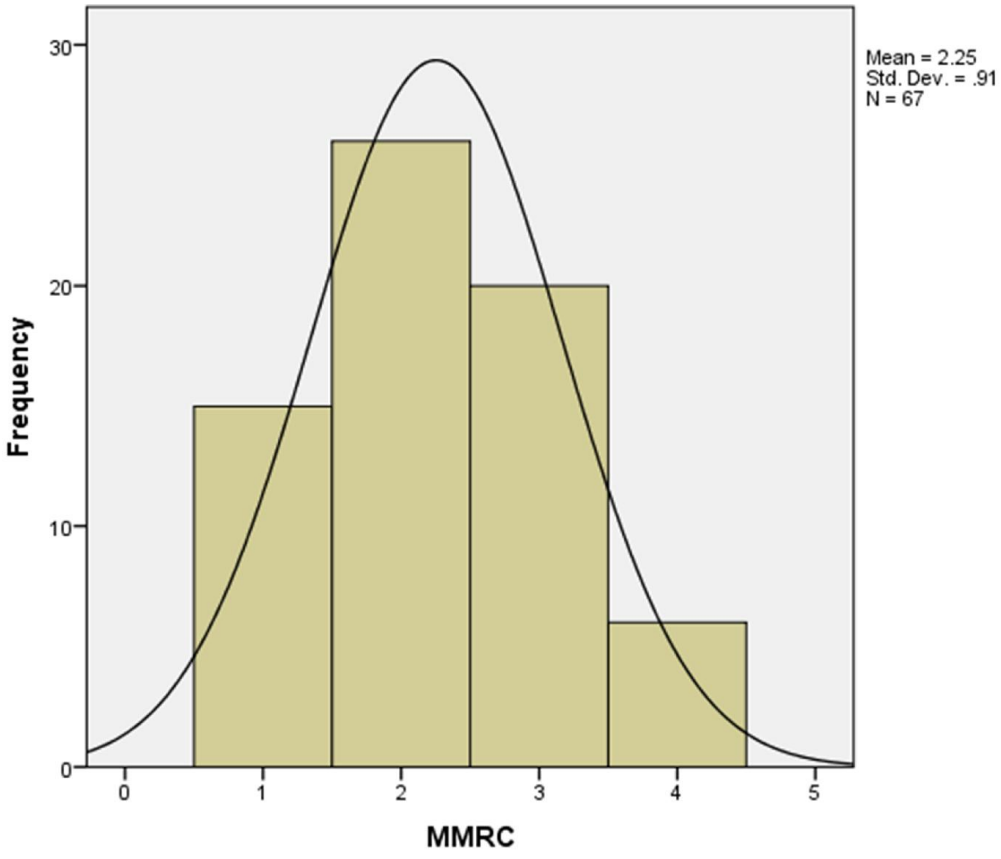


Figure 13: MMRC dyspnoea scale of the patient enrolled in the study. MMRC- Modified medical research council.

Most of the patients enrolled in our study belong to the moderate dyspnoea score (Figure 13). This is expected as the patients were all enrolled from the outpatient services. The sick patient with high MMRC score are generally admitted for further management.

BODE index

The BODE index was calculated for all patients. BODE index was grouped in to three categories.

- Less than 5
- Between 5 to 7
- More than 7

This categories is based on the previous studies relating BODE index to mortality risk at two years.

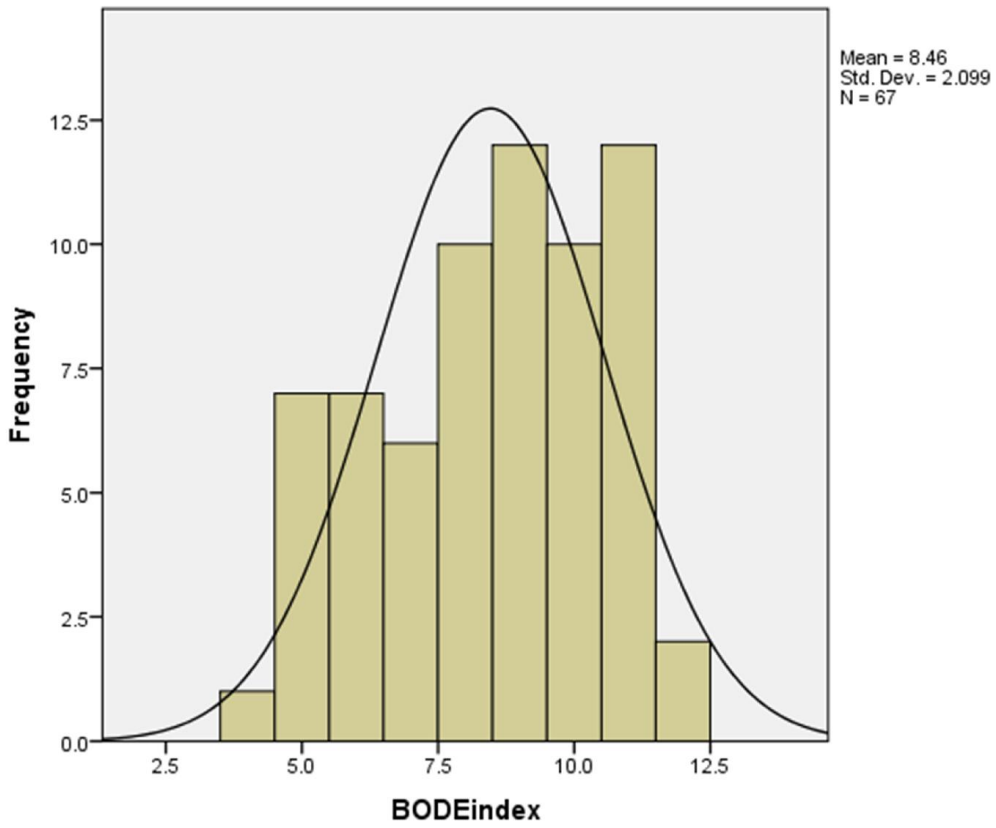


Figure 14: Histogram of the overall BODE score of the patient enrolled in the study (BODE stands for Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise)

Most of the patients were in the moderate severity (Figure 14). This score takes into account both the clinical parameters and the spirometry value. Hence it predicts the disease severity to greater accuracy than compared to the GOLD staging alone.

The frequency of patient in each category is as follows less than 5, 5 -7 and more 7 is 8, 7 and 52 patients respectively (Figure 15)

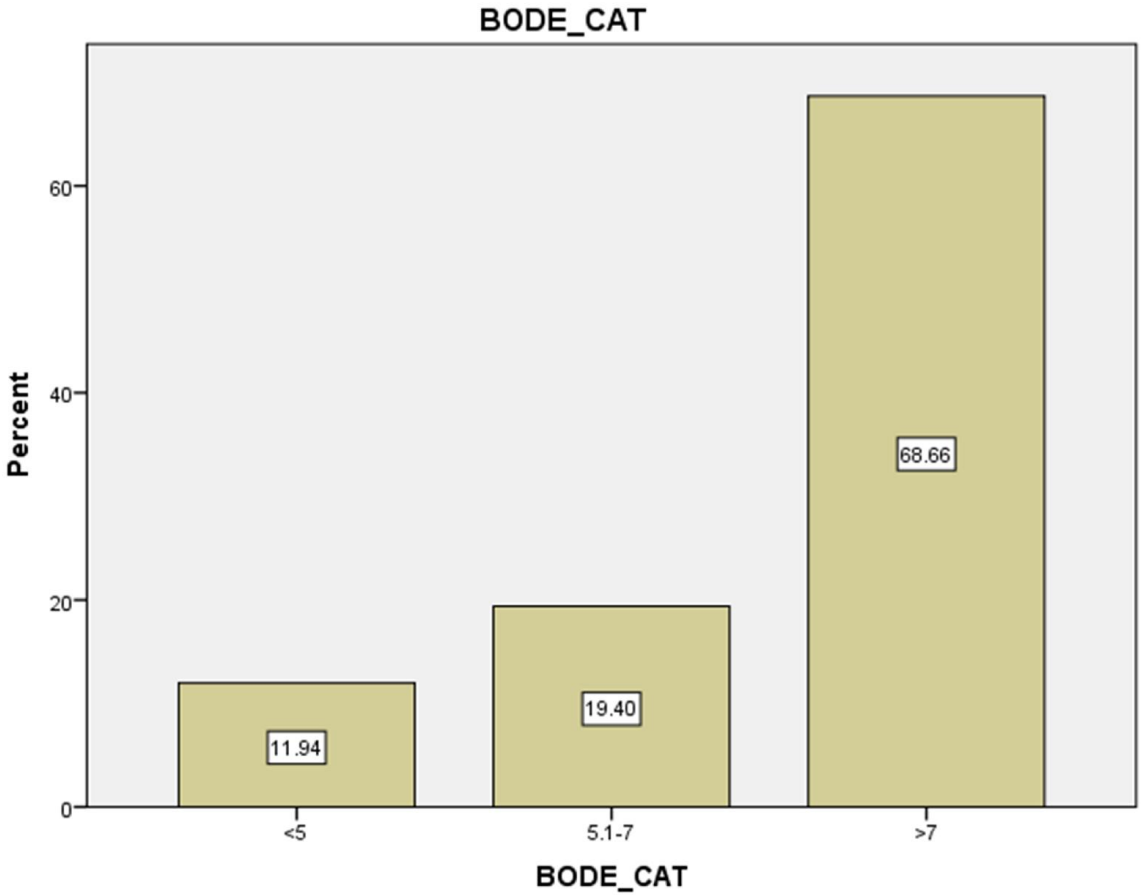


Figure 15: BODE index categorisation. The categories were based on mortality risk. The less than 5 have least mortality risk compared with more than 7. (BODE stands for Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise. BODE_CAT –BODE categorisation).

The mortality risk according to BODE index in each category is as follows

- greater than 7 is associated with a 30 percent 2-year mortality
- Score of 5 to 7 is associated with 15 percent 2-year mortality.
- less than 5, the 2-year mortality is less than 10 percent

Treatment characteristics:

Inhaled steroid:

All of them received inhaled steroids. The inhaled steroids were calculated for Budesonide equivalent dose. They were group into low dose and high dose category based on the daily cumulative steroid dose inhaled. The low dose category received daily cumulative dose of budesonide < 800 ug/day and high dose category received more than 800 ug/day. This classification is based on the TORCH trial which showed high dose patients are more prone for osteoporosis(64).

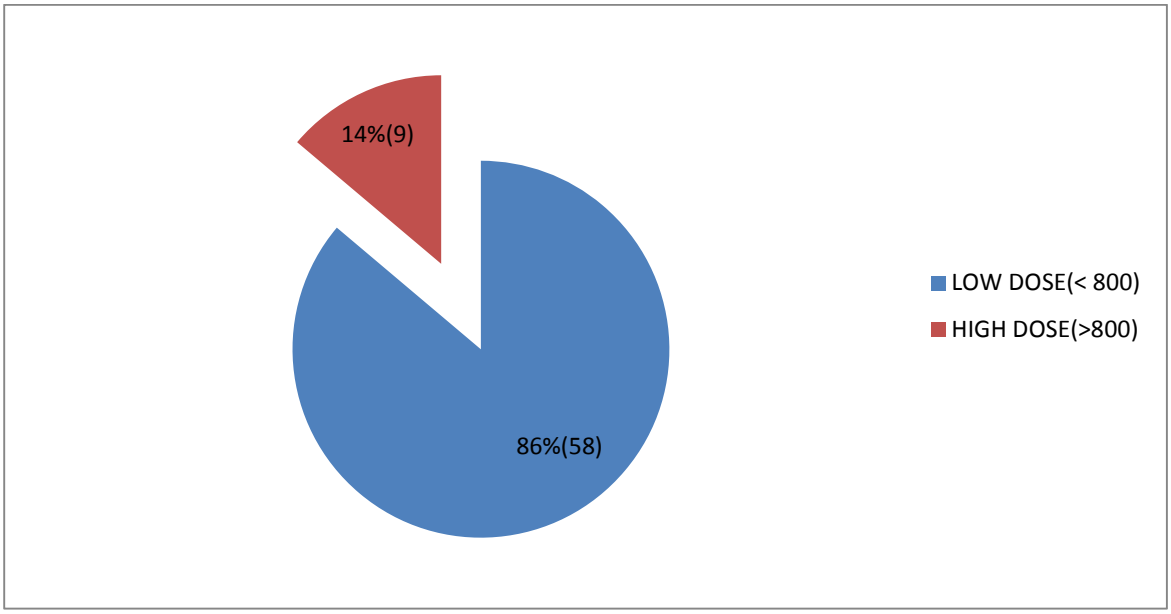


Figure 16: Daily cumulative dose of inhaled steroids (Budesonide equivalent) of the patient in the study

Only less than 10% of the patient received high dose steroids (Figure 16). This is accordance with the study population, as these are stable COPD patients whose disease are near optimally controlled.

Oral steroid

There were seven patients who received oral steroids in the last two years. The dose ranges from 5 to 120 days (Figure 17). These patients were in the stage III and IV disease and had high BODE index score.

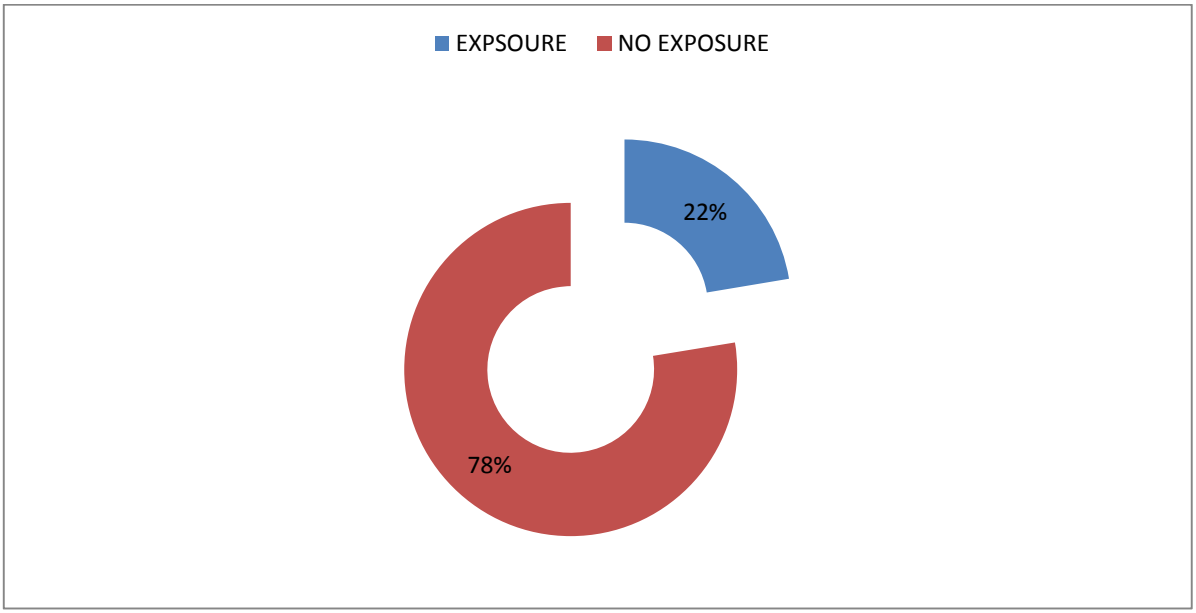


Figure 17: Percentage of the patient who took oral steroid during the study period

The oral steroids were calculated for prednisolone equivalent dose. Most of the patients' disease activity was controlled only with inhaled steroids. Only very patients had taken oral steroids.

Smoking status

The smoking status of the patient included in the study is as follows. There were 7 patients who were still current smokers (Figure 18)

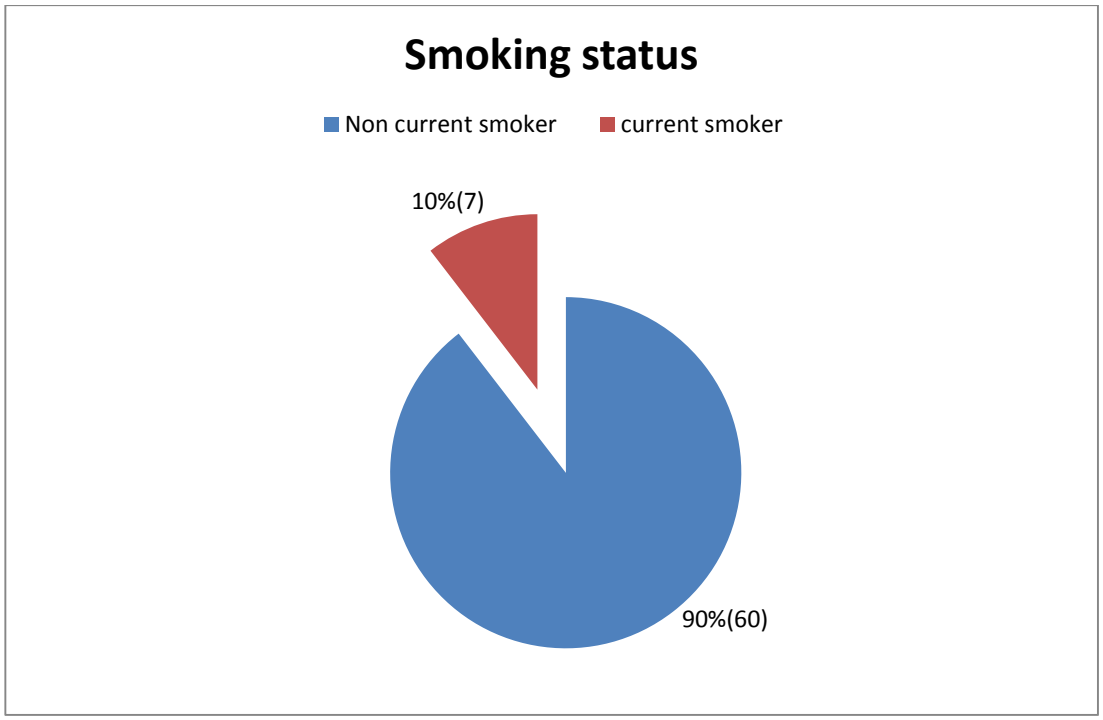


Figure 18: Smoking status of the population enrolled into the study

Of the 67 people recruited for the study, 7 patients were never smokers. Of the remaining 60 patients, 7 were current smokers. There were 40 patients who had significant smoking history of more than 20 pack years and 20 patients had less than 20 pack years of smoking (Figure 19).

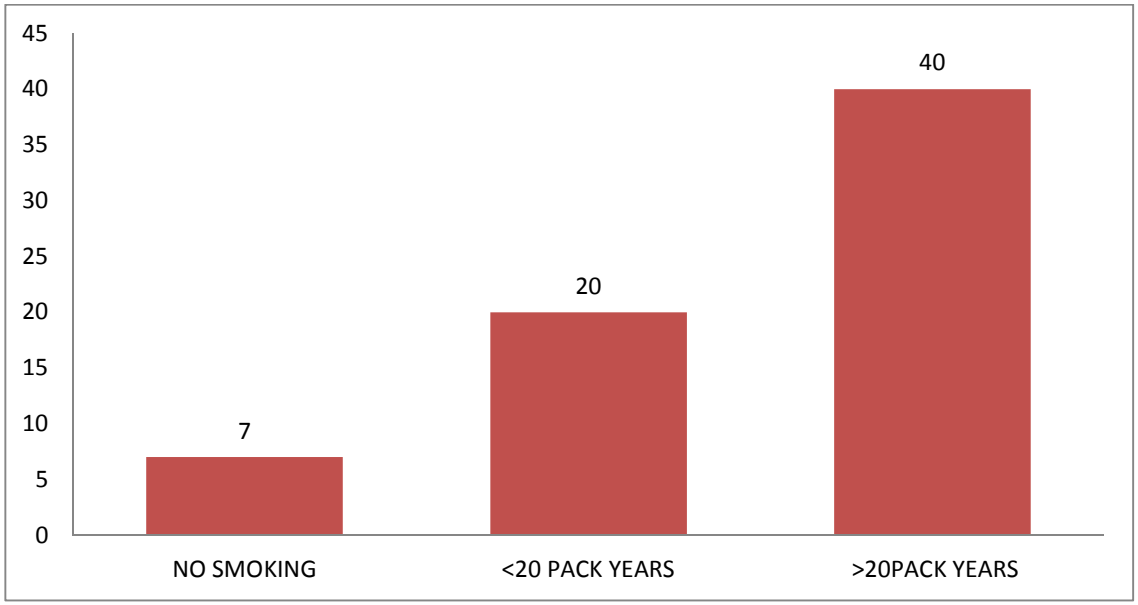


Figure 19: Duration of smoking of the study population

As expected most of the patient where in the more than 20 pack years category indicating that one of the main risk factors for the development of the COPD in the first place was significant active or passive smoking.

Co-morbidity

The patients were assessed for the presence or absence of other co-morbidities like Diabetes mellitus, systemic hypertension and dyslipidaemia. And the presence of this co-morbidities and the influence of the bone health is correlated later in the analysis

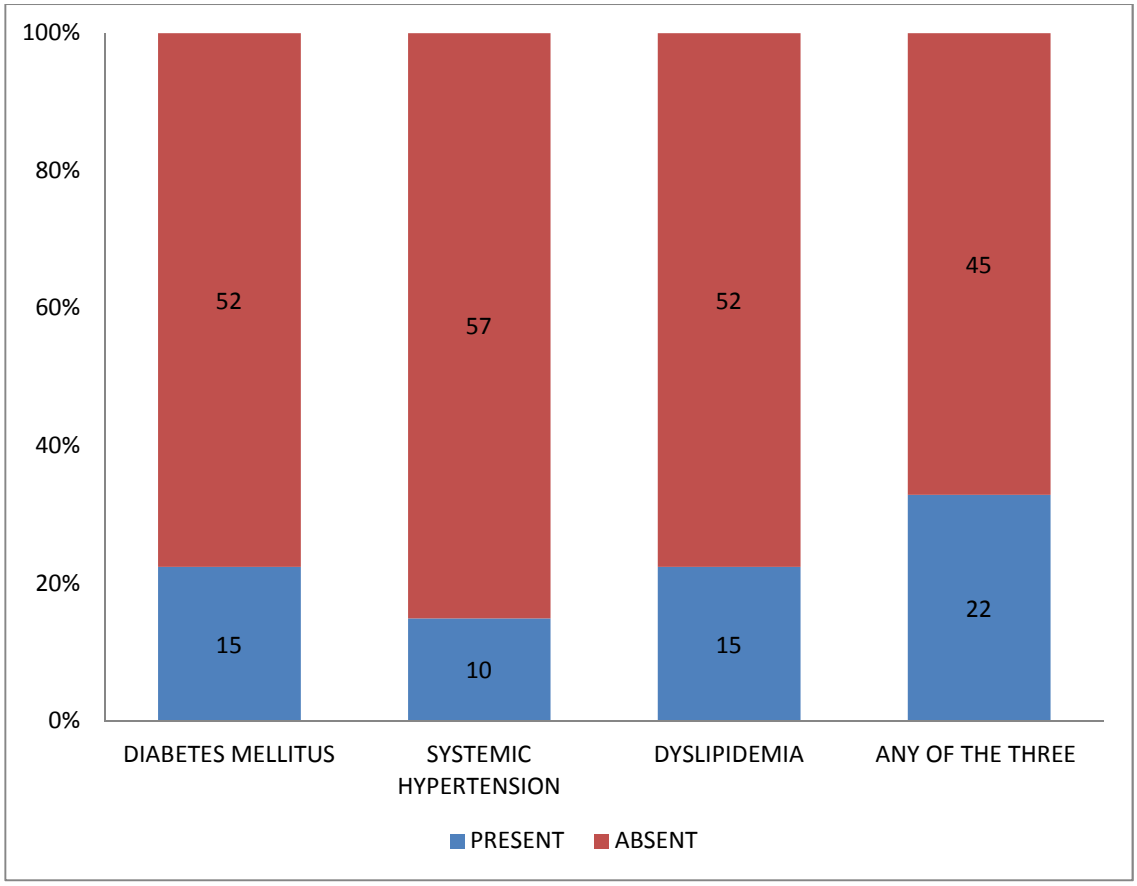


Figure 20: Presence of co-morbidities in the study population

There were 22(32%) in this study who had atleast one comorbidity (Figure 20). This again emphasising the point that patient with COPD have increased risk of systemic side effects either due to disease or due to treatment or both.

Andropause

The bone health is greatly influenced by the endogenous gonadal hormone. This relation is greater in women than compared with men. This is one of the reasons why all men were included in this study to rule out the effect of endogenous hormones. But even in men as explained previously there is significant contribution to decrease in bone mass by the declining testosterone level in the age more than 50 years. All patients were asked about the sexual history and the serum testosterone level was also measured (Figure 21). This is was done primarily to rule out any significant influence of andropause on the bone health of these patient

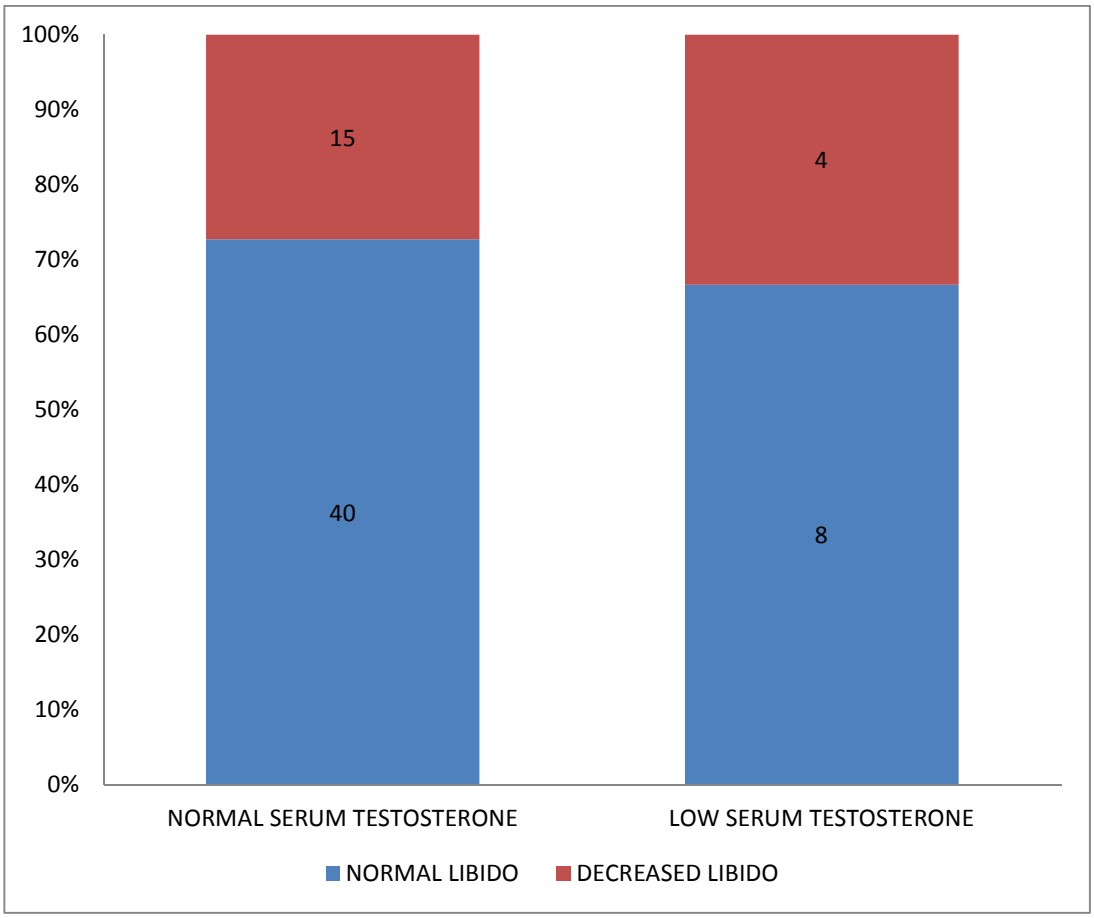


Figure 21: Comparison of the testosterone level with loss of libido

There was set of patient in our study who had low total serum testosterone level but had normal sexual function. This could be possible due to multiple reasons –normal free testosterone level, diurnal variation in the level of hormones and COPD affect the hormonal production but the receptor sensitivity to these hormones were increased.

Sunlight exposure and dietary calcium intake

The daily sunlight exposure was calculated as per method explained in the methods section and the 24 hour dietary recall method used to assess the dietary calcium intake. The daily recommended calcium intake is 1000mg per day.

The sunlight is one of the intermediate variables contributing the bone health of the patient with COPD. A decrease in sunlight exposure will result in decreased synthesis of vitamin D which has hormonal and extra-hormonal like action on the bone. The recommended duration of sunlight exposure from the previous studies were atleast 30 minutes per day such that the shadow formed due to the sunlight is more than the real size object. This is the early noon and late noon sunlight which has highest concentration of Ultraviolet B rays for Vitamin D synthesis.

The duration of the sunlight exposure recommended was more than 30 minutes per days. In COPD patients this may be restricted because of the restriction of outdoor activity due to dyspnoea, body composition and in the late stage due to the requirement of the oxygen.

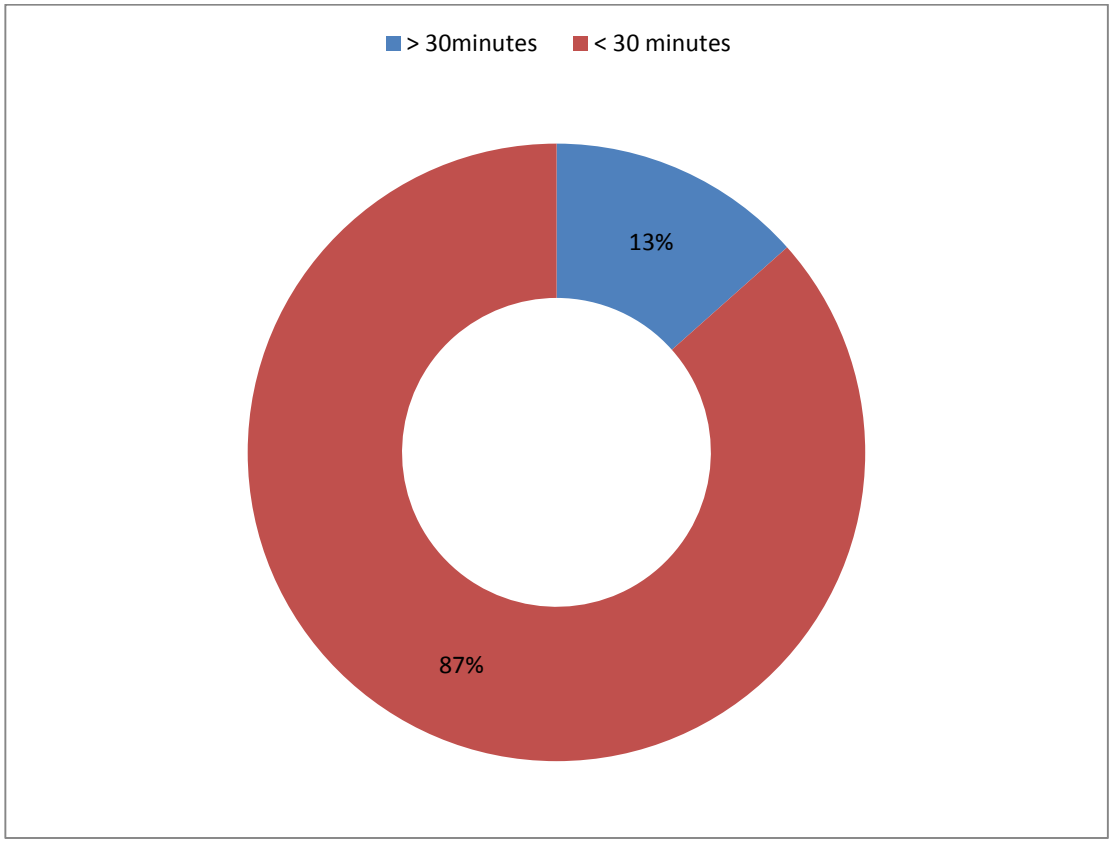


Figure 22: The sunlight exposure of the study population

Only less than 20 patients in our study had adequate sunlight exposure (Figure 22). This may be due to lot of reason. The restriction of outdoor activities as explained above. The dressing trends of the people in south India. The advanced age group of the patients enrolled in the study who generally carries covering like umbrella to cover from the sunlight when they go out to the sun.

The importance of the intake of the raw material for bone turnover was well emphasized in the discussion. The RDA (recommended daily allowance) for calcium intake for the Indians is 1000mg per day. The study population were classified into low and high calcium intake groups based on this cut off (Figure 23)

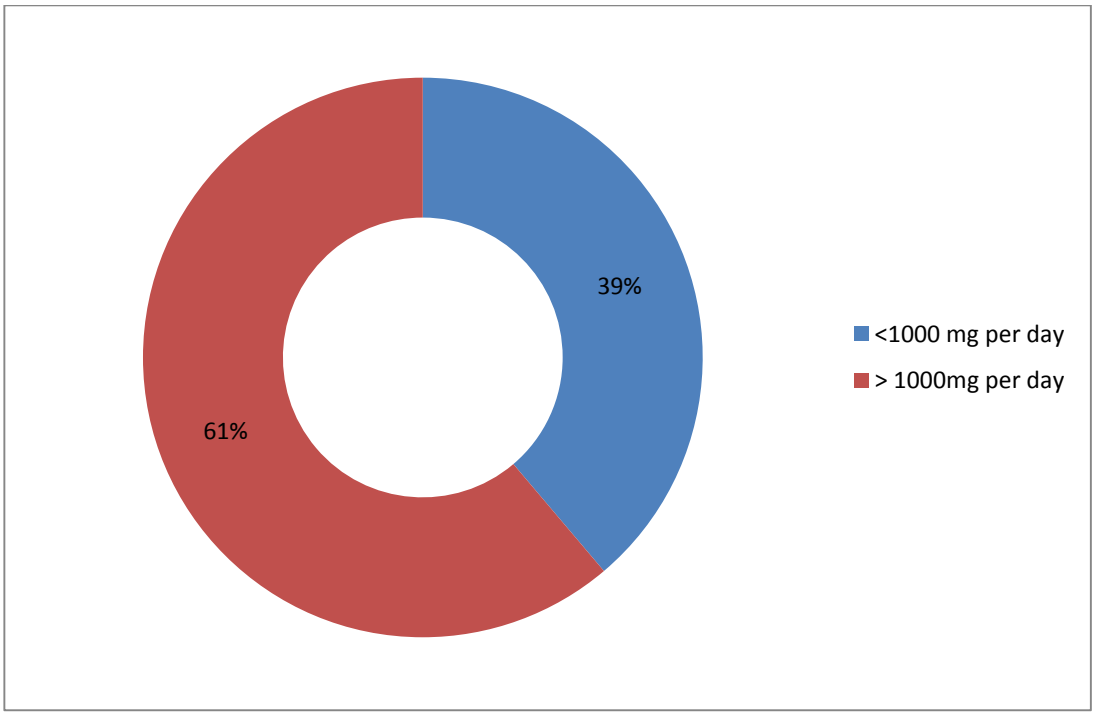


Figure 23: Dietary calcium intake of the study population

Anthropometric measures

The following table gives the important anthropometric measures of the population studied and their mean, median, standard deviation and range (Table 9).

Table 9 Anthropometric measures of the patient BMI- Body mass index, Hip-Hip circumference, WHR weight hip ration.

	Height cm	Weight kgs	BMI Kg/m2	Waist cm	Hip cm	WHR
Mean	163.13	61.29	23.00	88.23	89.50	0.98
Median	163	60	22.96	89	89	97.56
Std. Deviation	6.55	14.21	5.05	13.84	12.80	6.99
Minimum	143	33	13.1	41	31	85.1
Maximum	176	105	37.2	129	133	132.3

The mean BMI of the population studied corresponds to obesity cut off by WHO classification of obesity. But the studies among the Asian Indian suggest lower BMI cut off for normal. This BMI corresponds to the high normal range according to the specific cut off for the BMI. The normal WHR for Asians is less than 0.9.

Examination:

The study population underwent a focussed examination. The pulse rate, blood pressures were recorded and tabulated as line plot (Figure 24)

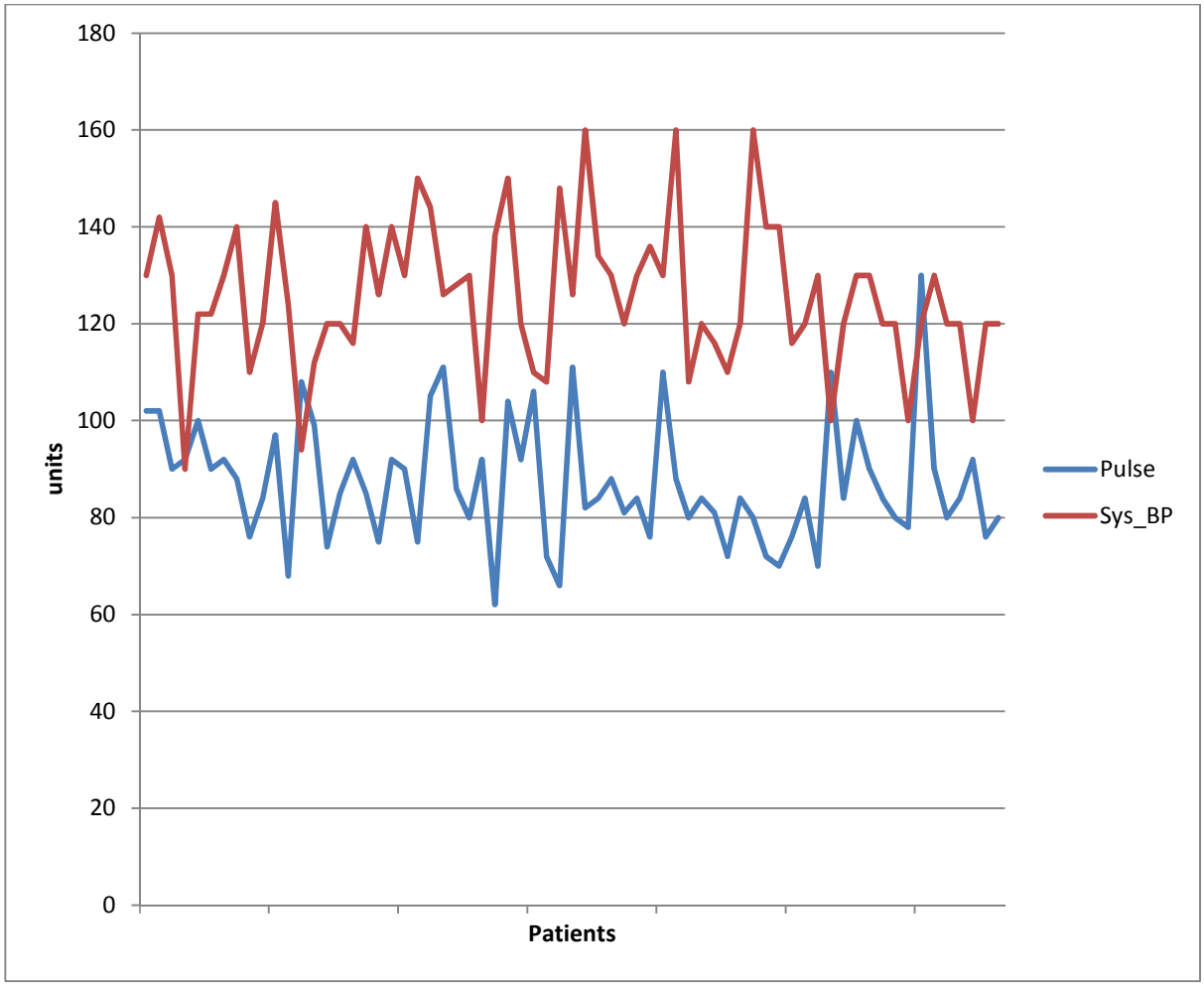


Figure 24: Blood pressure and Pulse rate of the study population. (Sys_BP – Systolic blood pressure in millimetres of mercurey, Pulse- pulse rate per minute.)

Most of the study patients' vitals were in the normal range, but the tachycardia in few patients is attributed to the high dose inhaled beta agonist along with high dose corticosteroids**.**

Laboratory parameters related to bone health:

Patients who were included in the study underwent detailed laboratory assessment too. Their serum vitamin 25 OH-vitamin D3, which one of the important contributors to the bone metabolism was measured and was plotted (Figure 25).

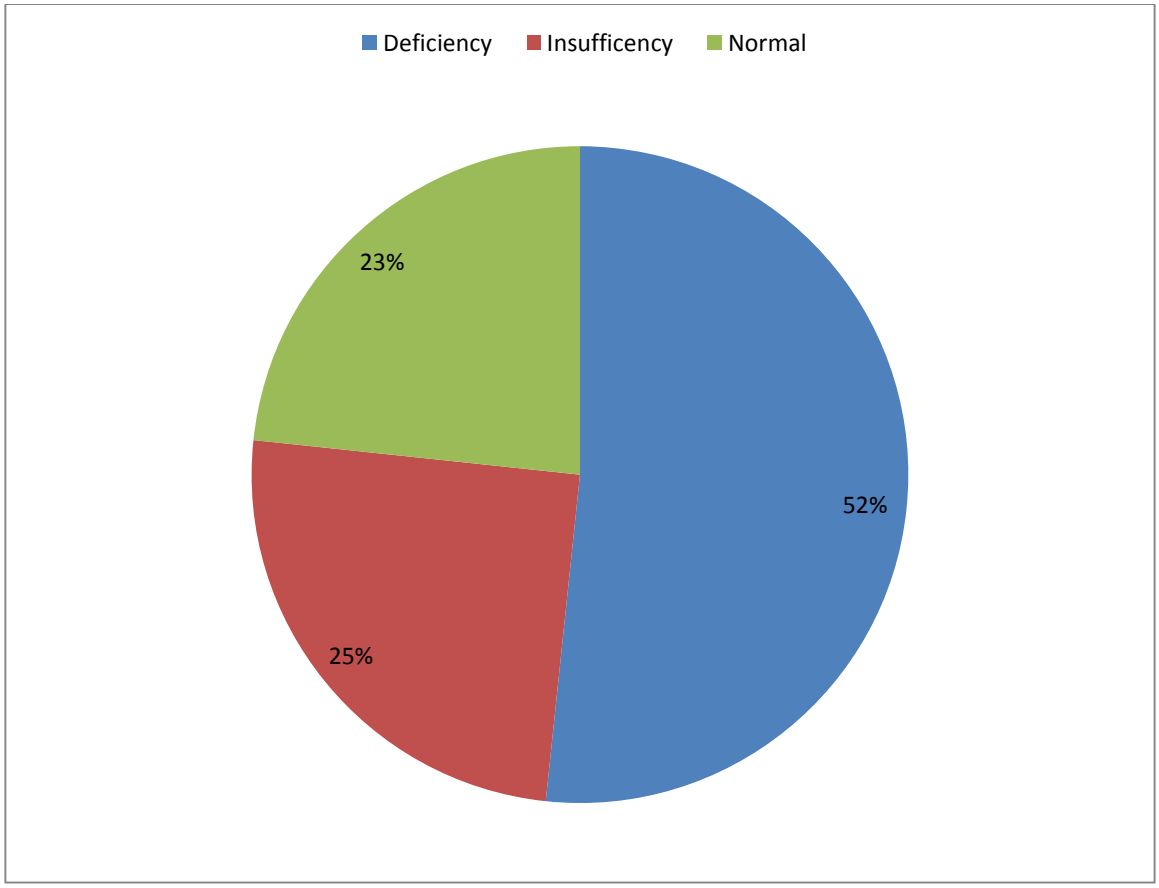


Figure 25: 25-hydroxy vitamin D3 of the study population. Serum level more than 30 ng/mL is taken normal. Levels between 20-30 ng/mL is taken as insufficiency and less than 20 ng/mL is taken as deficiency.

The patients included in the study underwent early morning blood sample for serum calcium, iPTH and 25-hydroxy vitamin D levels (Figure 26). The samples were collected without

tourniquet to avoid falsely high calcium level. The calcium was corrected for the serum albumin and the corrected calcium was used for analysis.

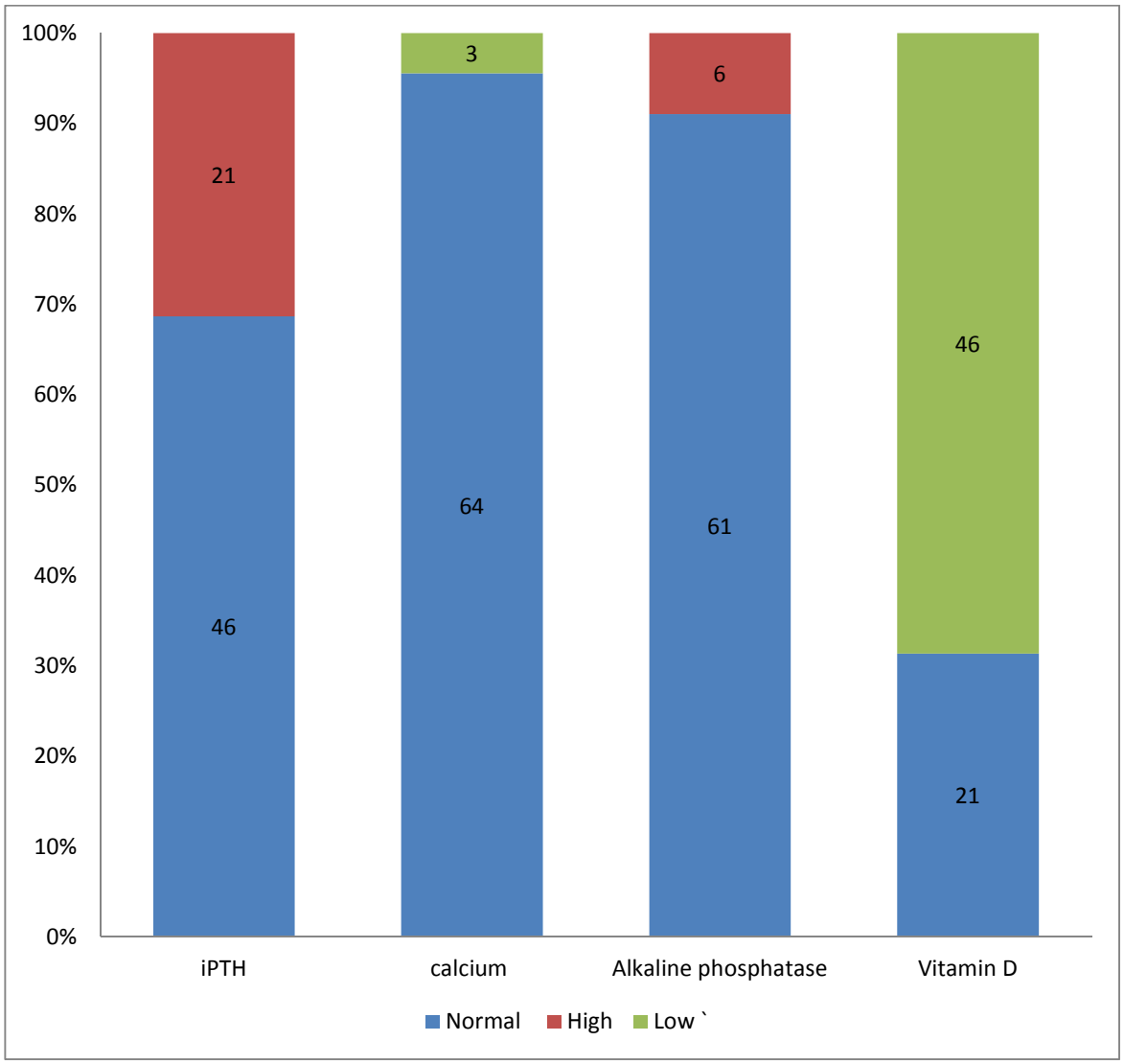


Figure 26 Serum levels of iPTH, Calcium, alkaline phosphatase and vitamin D across the study population, iPTH-intact parathyroid hormone, vitamin D- 25-hydroxy vitamin D3

As excepted 25-hydroxy vitamin D levels were low. But we also found increase in the serum iPTH level in 31% of the patient. The reason for this could be due to severe vitamin D deficiency with secondary hyperparathyroidism.

PRIMARY OUTCOME

Primary outcome

The overall study outcome of osteopenia and Osteopenia in the COPD patient is shown below bar diagram (**Figure 27**)

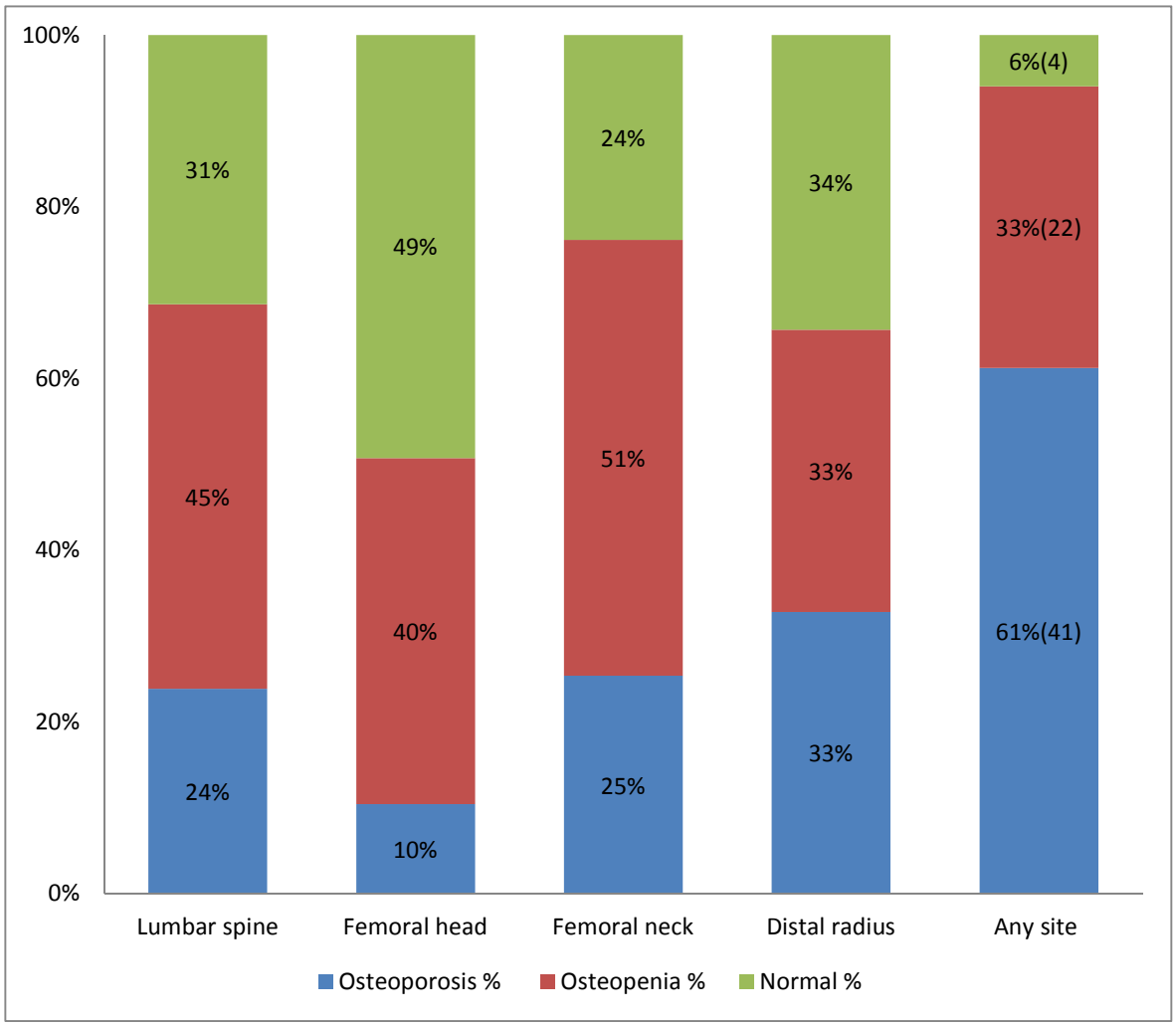


Figure 27: Prevalence of low bone mineral density-osteoporosis and osteopenia. Overall prevalence of osteoporosis in this study is 61%

This result is again show in the form of table (**Table 10**) to emphasize the fact that the prevalence of osteoporosis in this study was as high as 61 **percent(41/67)** i.e. one in two patient with COPD who visits the ambulatory care of the tertiary care centre are osteoporotic.

Table 10: Prevalence of osteoporosis in patients with COPD. The numbers represent the actual number of patient. N=67

Regions	T score <-2.5	T score -1 to -2.5	T score >-1.0
Lumbar spine	16	30	21
Femoral head	7	27	33
Femoral neck	17	34	16
Distal radius	22	22	23
Any site	41	22	4

CORRELATION OF LOW BONE MINERAL DENSITY (OSTEOPOROSIS AND OSTEOPENIA):

The low bone mineral density is correlated with various predictors of adverse bone health

- Age and osteoporosis
- Smoking and bone health
- Duration of COPD
- Sunlight exposure and BMD

- Dietary calcium intake
- Stage of COPD
- BODE severity index
- Inhaled steroid
- Oral steroid

First the prevalence of these abnormalities together is described and then the significance level is described by appropriate statistical test.

Age and osteoporosis:

The prevalence of the osteoporosis increase as the age advances. This was studied and the age distribution of the patient was characterised in to two groups: more than 60 years and less than 60 years. And as the age advance there was increased prevalence of osteoporosis even in our study (**Figure 28**).

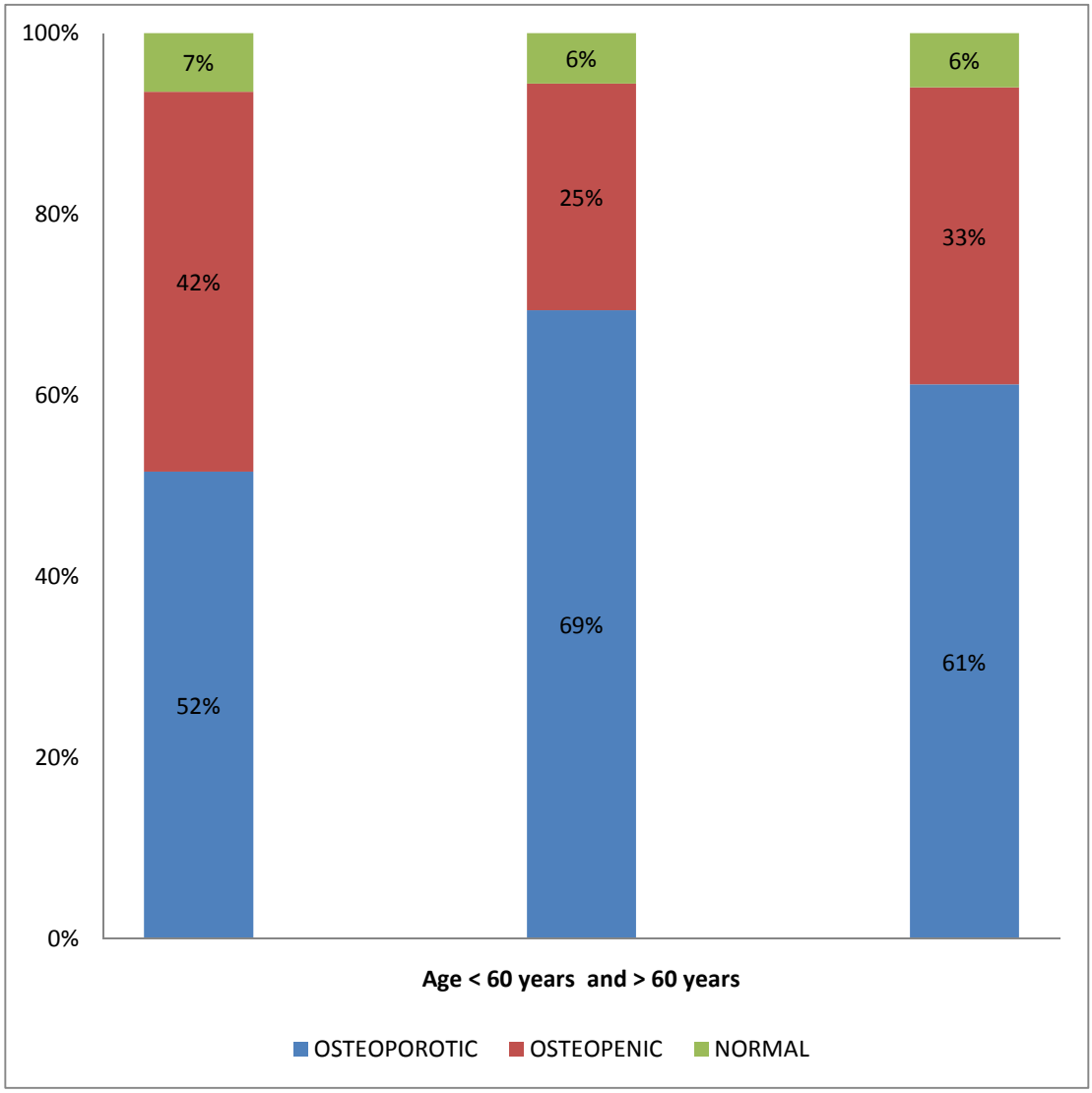


Figure 28: Age and low bone health correlation. Increase in age increase the prevalenc of the osteoporosis.

Effect of smoking and bone health:

The patient who were current smokers and reformed smokers were classified according to number of pack years and are divided into two categories as explained above and was then compared with bone mineral density (**Figure 29**)

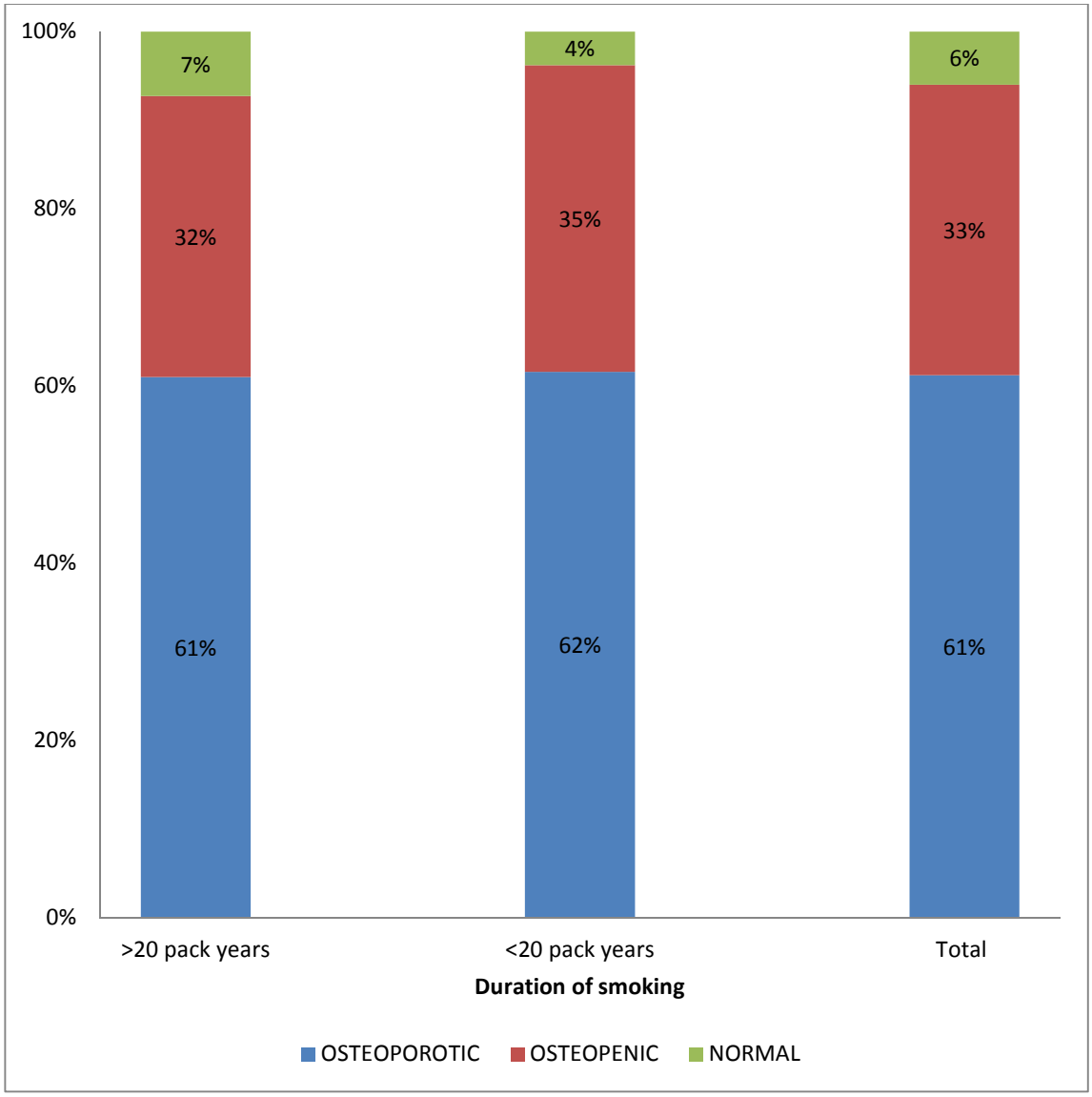


Figure 29: Smoking and bone mineral density correlation. Increase in smoking shows increasing trend toward adverse bone health

Duration of COPD and BMD:

Longer the duration of disease, the more common is the systemic side effect. This is especially true for chronic disease like COPD. (**Figure 30**)

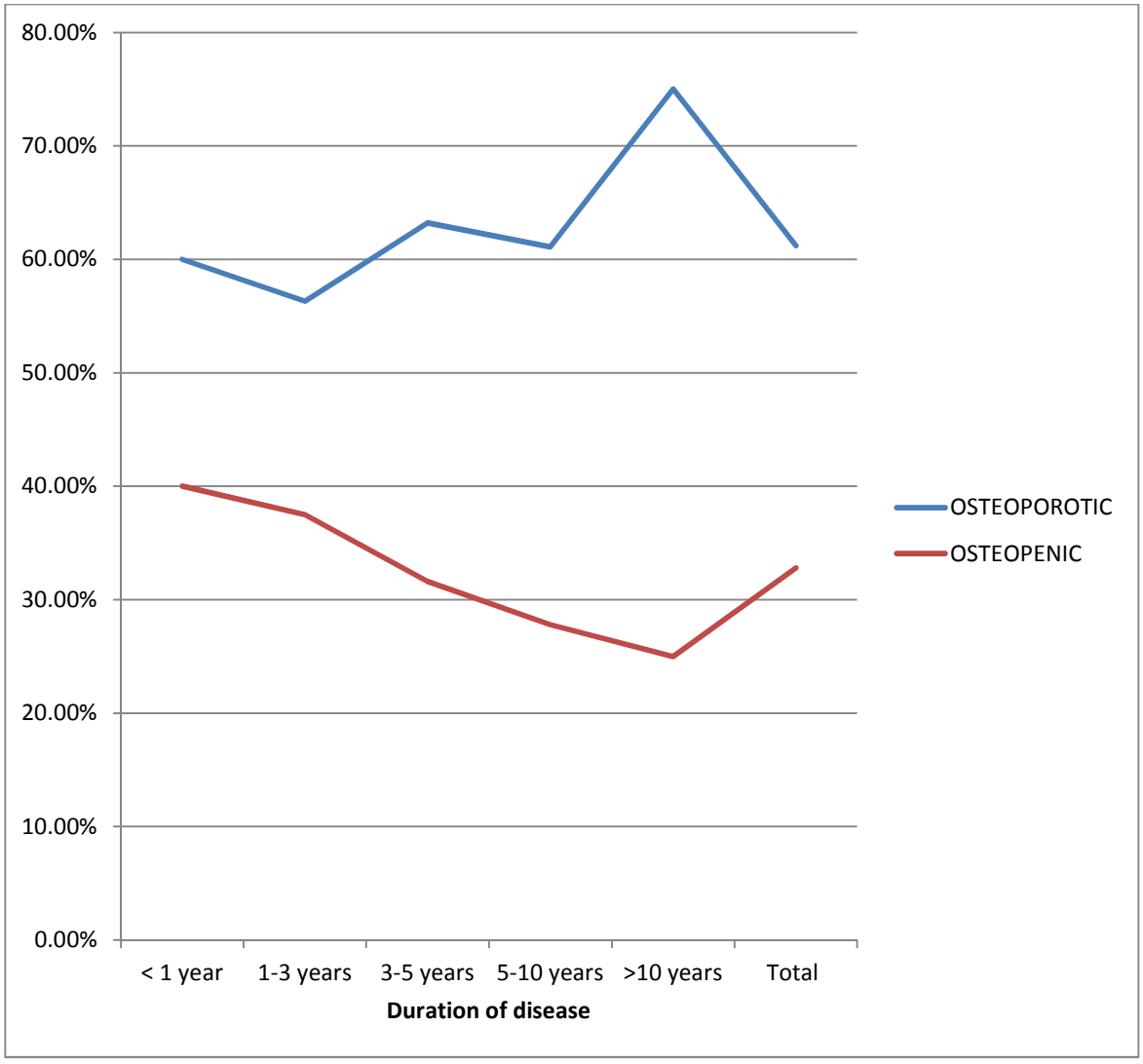


Figure 30 Duration of COPD and bone mineral density correlation. Increase in duration of the disease show a trend towards increasing adverse bone health

Effect of sunlight exposure and osteoporosis and osteopenia:

There is significant proportion of patient who did not have adequate sunlight exposure. The sunlight exposure is calculated according to method describe above in the methods sections.

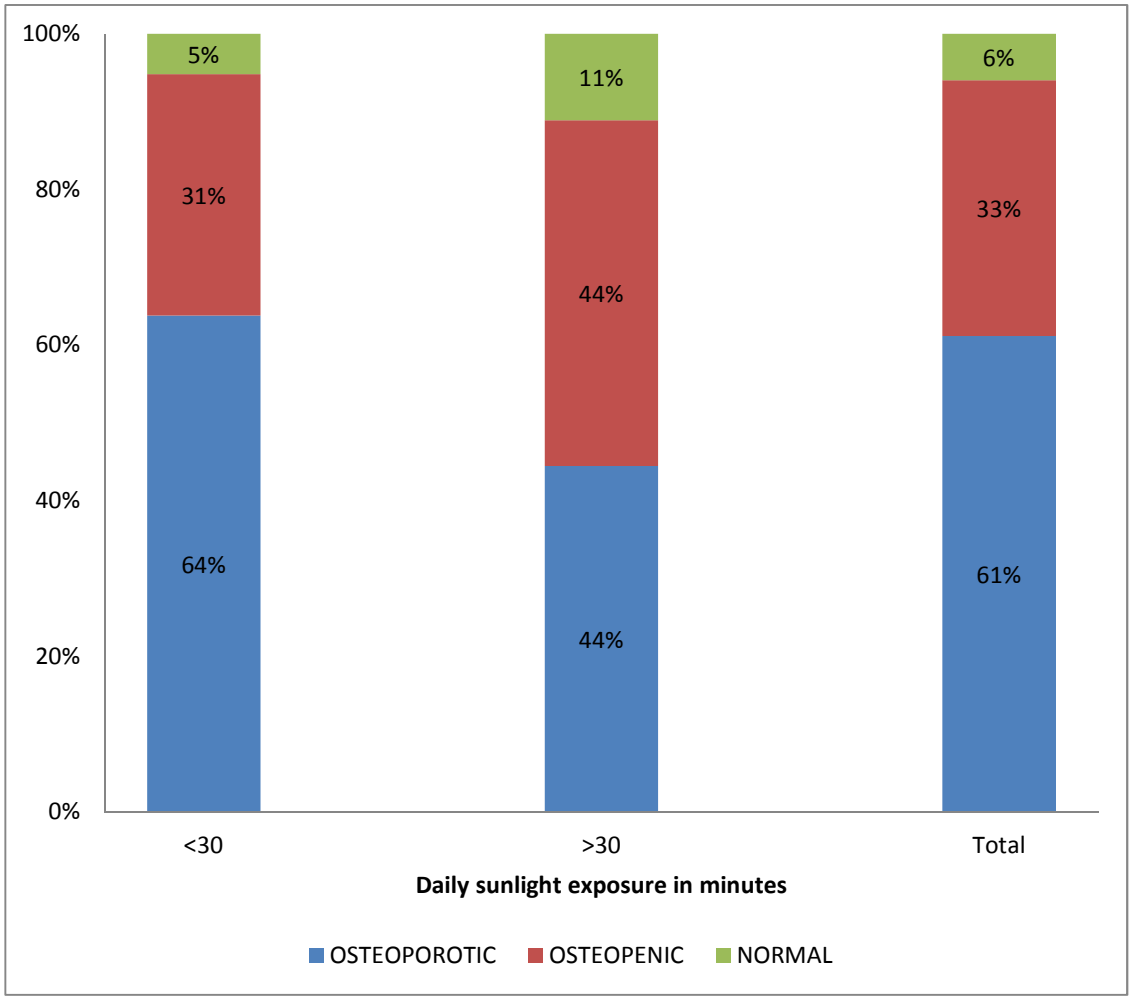


Figure 31: Daily sunlight exposure and bone health correlation. <30 -less than minutes per day and > 30- more than 30 minutes per day

There is a positive correlation between the amount of sunlight exposure and the bone health. In the group less than 30 minutes there is increasing trend towards more patients with osteoporosis and osteopenia (**Figure 31**).

Dietary calcium intake and osteoporosis:

The dietary calcium intake was calculated according to the 24 hours dietary recall method. The dietary intake of calcium is the necessary raw material for the adequate bone strength.

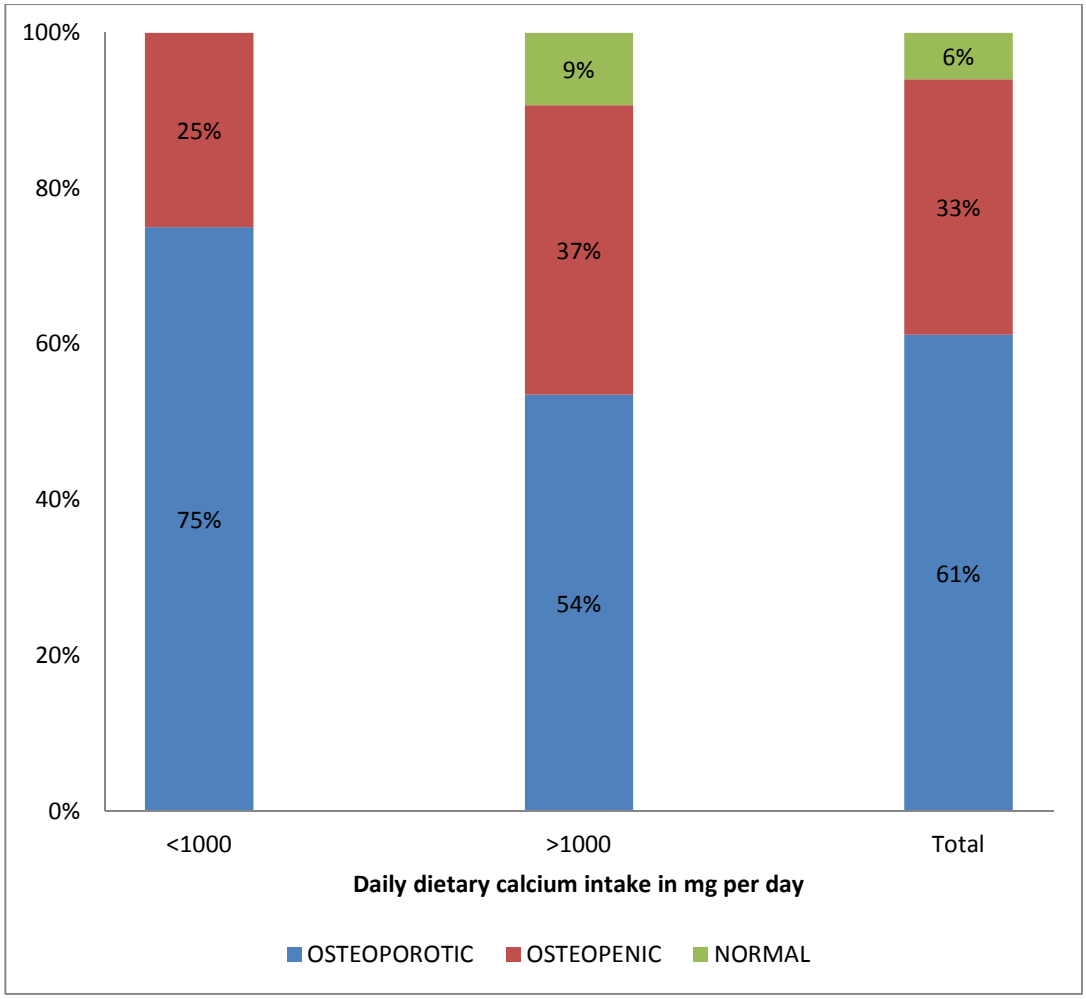


Figure 32: Dietary calcium intake and bone health correlation

The low dietary calcium intake was positively correlated with poor bone health (**Figure 32**). Although the dietary intake is less but there was only very small number of patient with hypocalcaemia. This may be due to method used to assess the dietary calcium intake. The more appropriate would to measure urine calcium and assess the calcium balance.

Disease severity and osteoporosis:

The correlation of disease severity contributing to the systemic side effects is due to two main reasons:

- Increased systemic spill over of the inflammation
- Increased used of steroid to control the disease

The severity of the disease is estimated based on two things GOLD staging (**Figure 33**) and the prognostic index is the BODE index (**Figure 34**).

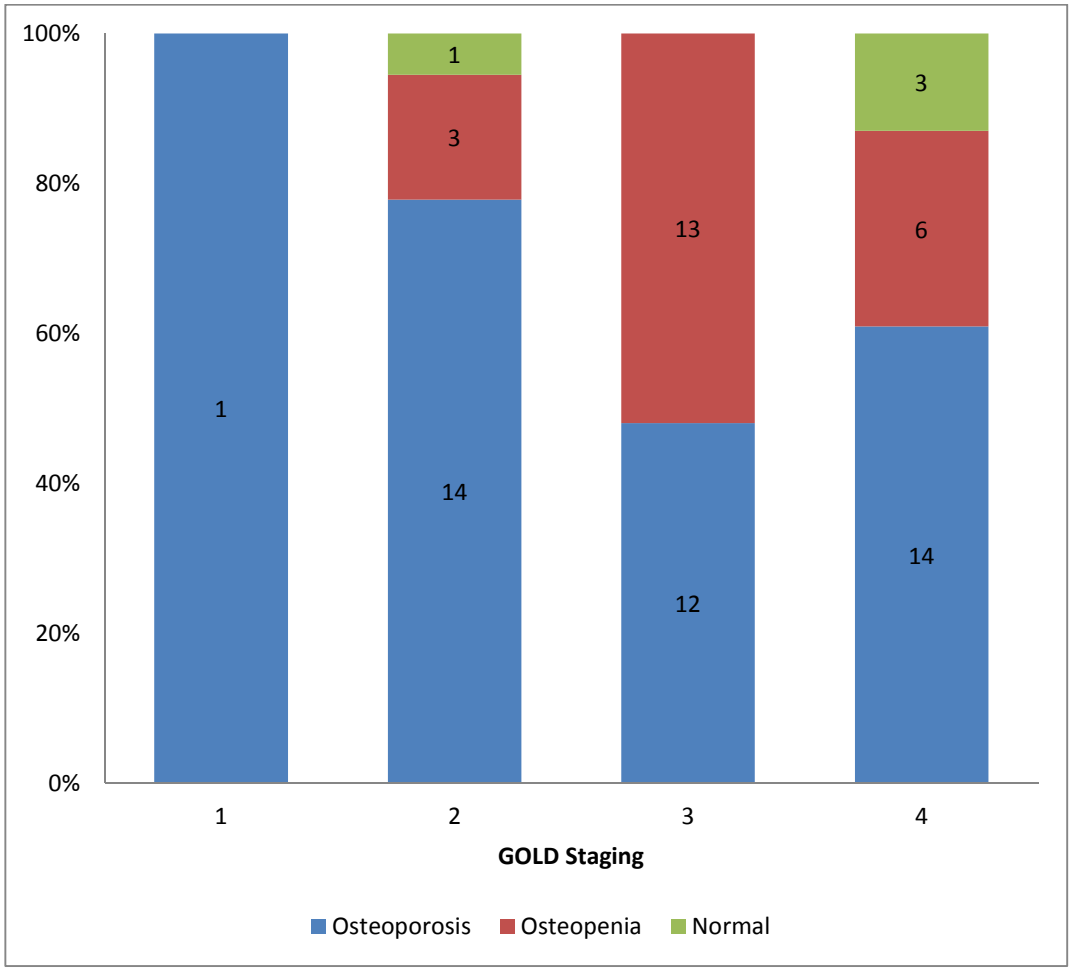


Figure 33: GOLD staging and bone mineral density correlation.

The better predictive scoring is the BODE severity index which associates disease severity with the mortality at two years. As the disease severity increases, there is increase in the complications as expected (**Figure 34**)

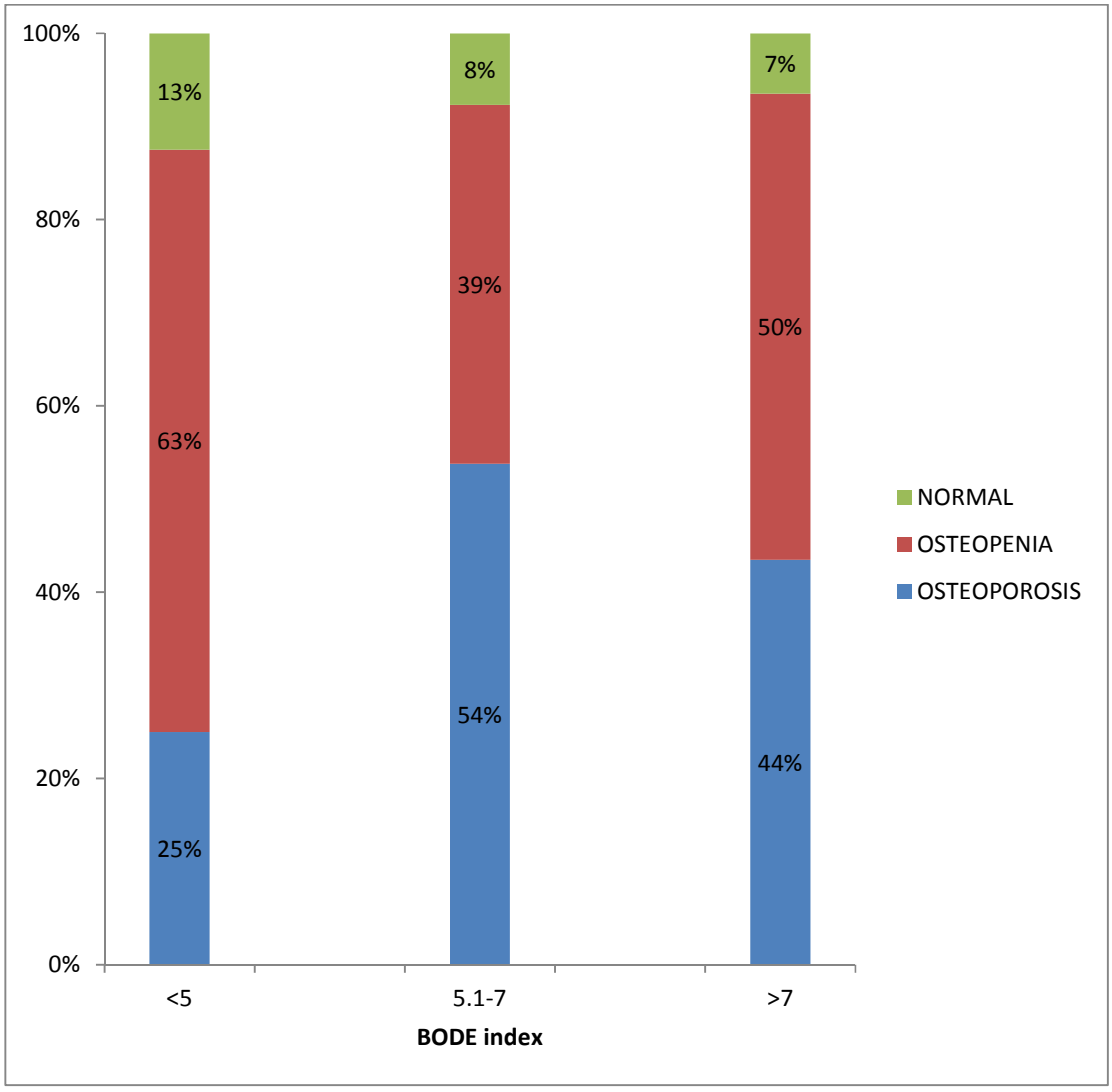


Figure 34: BODE severity index and osteoporosis correlation

Treatment and BMD correlation:

It was previously seen in the above discussions that the dose of inhaled steroids was positively correlated with osteoporosis. In this study we noticed the similar trend

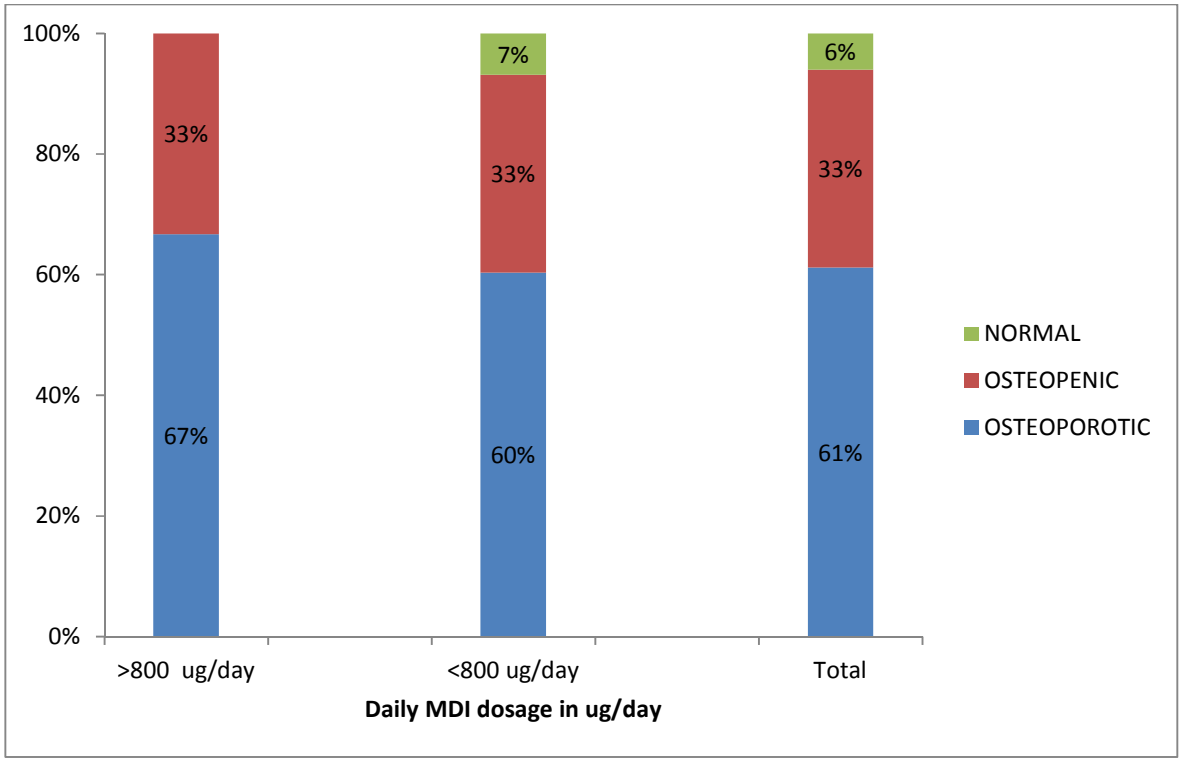


Figure 35: Inhaled steroid cumulative daily dose with severity of bone health. MDI-metered dose inhaler.

As the daily steroid intake increase there is a positive correlation with poor bone health. This is because higher dose are used in more severe patient, these patient tend to have more severe systemic complication and increase systemic spill over of the inhaled steroids (**Figure 35**).

This is also true for the total lifetime dose of inhaled steroid intake. The total lifetime dose of steroid intake is positively correlated with the increased risk of osteoporosis and osteopenia (**Figure 36**)

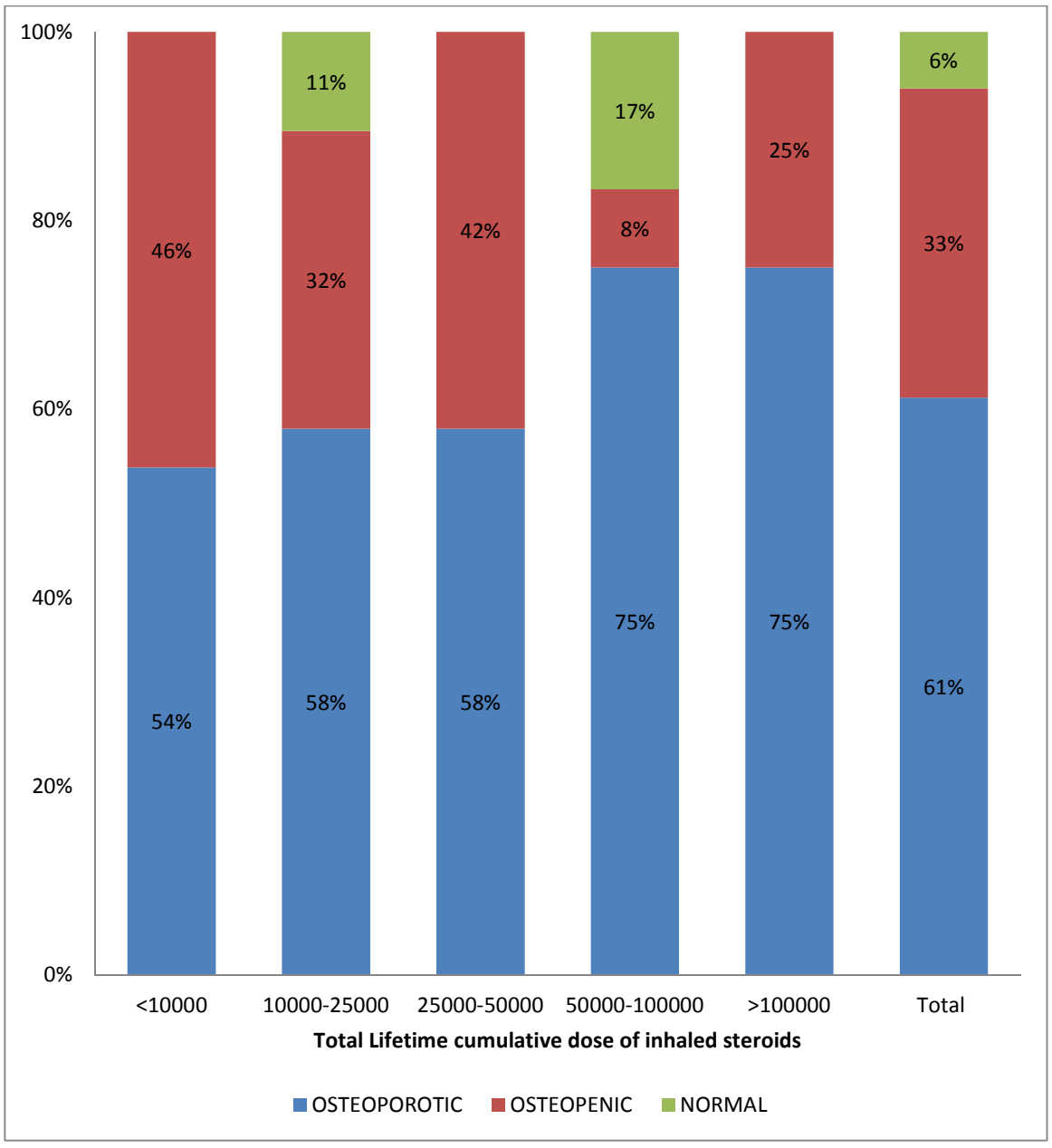


Figure 36: Cumulative lifetime steroid intake and the prevalence of osteoporosis and osteopenia

The increased risk for osteoporosis with increased cumulative steroid intake may be due to multiple reason- increased duration of disease, difficulty in controlling the symptoms and erinaceous prescription of medicine

Oral steroids

The intake of oral steroid increases the adverse systemic complications one of which is osteoporosis (**Figure 37**). The intake was high in poorly controlled disease, refractory COPD and frequent exacerbation

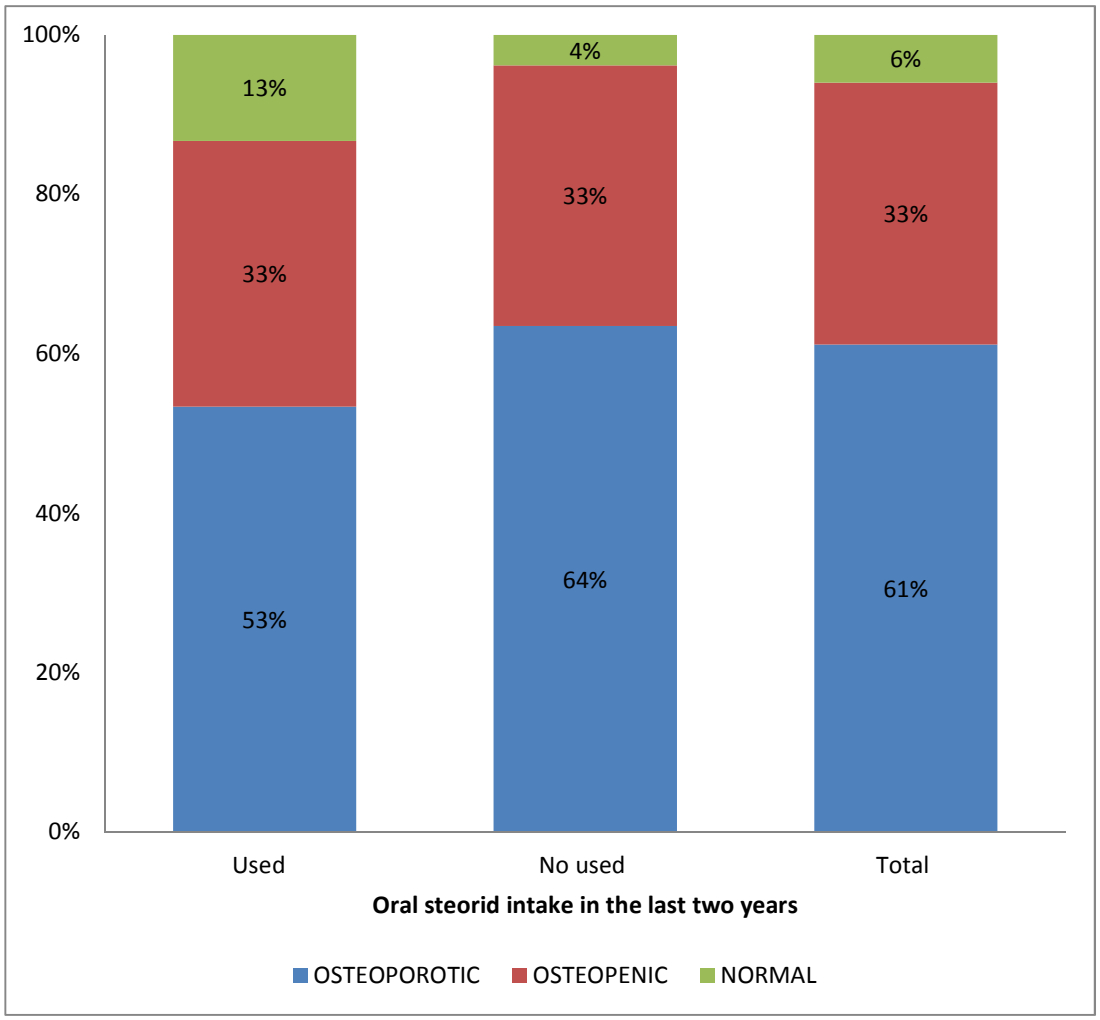


Figure 37 oral steroids and bone health correlation

Statistical test of significance

All the parameters which showed increased prevalence among the COPD patient were included for test of significance. Pearson correlation –r and the t tailed p, was calculated. (**Table 11**)

Table 11 two tailed p value for the bone mineral density

Categories	LS spine	Femoral neck	Femoral head	Distal radius
Age	0.182	0.192	0.409	0.019
BMI	0.003	0.000	0.001	0.001
Smoking	0.405	0.214	0.873	0.576
Inhaled steroids	0.833	0.542	0.423	0.800
Oral steroids	0.408	0.621	0.631	0.726
Sunlight exposure	0.870	0.193	0.431	0.160
Dietary calcium intake	0.723	0.277	0.461	0.553
BODE index	0.625	0.234	0.407	0.949
GOLD stage	0.063	0.345	0.439	0.868

Person chi square test was performed with two tailed p value. The odds ratio and confidence interval were calculated

Table 12: Multivariate analysis of the variables associated with adverse bone health bone health. (C.I. – 95% confidence interval)

Categories	chi-square	p-value	odds ratio	C.I.
Age	2.23	0.208	0.469	0.173-1.275
Inhaled steroids **High vs. Low dose**	0.131	1	1.314	0.298-5.787
Oral steroids	0.503	0.553	0.658	0.206-2.101
Smoking pack years **(<20 Vs. >20 pack years)**	0.002	1	0.977	0.356-2.678
Sunlight exposure **(<30 Vs. > 30 minutes)**	1.228	0.294	2.202	0.533-9.108
Dietary calcium intake **(<1gm vs. > 1gm/day)**	3.002	0.118	2.609	0.867-7.847
GOLD Stage	3.502	0.094	0.315	0.091- 1.09

Chi square test was performed and none of the variable which showed increased prevalence among COPD patient with osteoporosis in the previous analysis showed statistical significance (**Table 12**). This may be because of the small sample size which requires large study at a later date.

DISCUSSION

DISCUSSION

COPD is a systemic disease as established by the number of previous studies(1). Although the most serious extra-pulmonary organ involvement is the cardiovascular system but the most common disorder is the metabolic disorder. The poor bone health in patient with COPD is risk factor for increased osteoporotic fracture as shown by the data from the TORCH trial(64). The problem with defining the risk for osteoporosis depends on loco- regional food habits, life style factors and the disease per se in view of environment pollution. To our knowledge this study was first to describe the all the parameters related to the adverse bone health in patient with Chronic obstructive pulmonary disease. This study clearly shows the increased prevalence of osteoporosis in COPD patient. This is almost doubled the prevalence as seen in normal population in India(65). In the following discussion we will enumerate the following in detail

- Prevalence of osteoporosis
- Predictors of osteoporosis
- Diagnosis of osteoporosis
- Treatment of osteoporosis in COPD

Prevalence of osteoporosis in COPD:

The prevalence of osteoporosis in our study was 61% this was almost equal to the prevalence that was obtained from the studies in India and in the western population(61–63). The bone density was measured at four place distal radius, femoral head, femoral neck and lumbar spine in our study. According to WHO if the T –score at lumbar spine or femoral neck less than -2.5 it is defined as osteoporosis in the men above 50 years of age (24). The prevalence we obtained

in our study is similar to the prevalence in the two studies published so far in India. The first one is the study done by Bhattacharya et al from Kolkata which was done in 2011(62). The following are important conclusion from the study

- Total of 37 patient with COPD were studied
- Patients were in stage III and IV disease
- Ultrasound bone densitometer was used for analysis

The limitations of this study was already been discussed. Osteoporosis was present in 19 (51.35%) and osteopenia in 8 patients (21.62%). According to the author the prevalence of the osteoporosis was high as compare to the prevalence of osteoporosis in the same region in the normal subjects.

The second Indian study which I am going to quote is the study done by Hattiholi et al from Karanataka (63). This study had the following characteristic features in compare and contrast to our study.

- 102 COPD patients both male and female were included.
- Prevalence of osteoporosis was 66.6% and osteopenia was 19.36%.
- BMD measured at Lumbar spine using DXA bone densitometer.
- Patients with low BMI, and female sex had increased risk for osteoporosis.

There were lot of limitation with respect to this study. The study population included both female and male. Female gender was one of the predictive variables for increased prevalence for osteoporosis. There was no sensitivity analysis done. The prevalence of osteoporosis in

ambulatory post-menopausal women in India according to the study done by Paul et al is 48% at the lumbar spine. This is the major limitation as this factor would have skewed the result to increased prevalence of osteoporosis in the patient with COPD. The prevalence of osteoporosis is similar to what we had found in our study corrected for the methodological problems in the previous studies. This is similar to the multiple studies that were published from all over the world (**Table 13**).

Table 13: Details of the studies in the western countries about the prevalence of osteoporosis and osteopenia in patient with COPD

No.	**Year**	**Proposed theme of the study**	**Authorsand reference**	**Study Design & Sample size if relevant**	**Prevalence of osteoporosis and osteopenia**
1	2007	The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease	Jørgensen et al(55)	Cross-sectional study 54 patients	23.7% and 40.7%
2	2005	Bone density improvement after lung volume reduction in COPD emphysema subjects	Mineo et al(66)	Prospective cohort study	35% and 49%

3	2003	Should COPD patients be routinely evaluated for bone mineral density?	Karadag F et al(67)	Cross sectional study 28 patient	35% and 42%
4	2008	. Cytokines, bone turnover markers and weight change in lung transplant candidates	Forli L et L(68)	Cross sectional study 40	48% and 33%
5	2004	Associated loss of fat-free mass and bone mineral density in COPD patients	CE Bolton et al(69)	Cross sectional study 80	27% and 38%

6	2002	Osteoporosis before lung transplantation	O Tschopp et al(70)	Cross sectional study 16	Osteoporosis 69% and osteopenia not reproted
7	2007	Low bone mineral density in COPD	Vrieze et al(71)	Cross sectional study 115	8.7% and 40.9%
8	2009	TORCH trial	Ferguson GT et al(64)	Prospective study 658	18% and 42 %

In all the above mentioned studies few important conclusions can be drawn

- Prevalence of osteoporosis varies between different population studies
- Prevalence of osteoporosis and osteopenia is in the range of 9-69% and 27-67% respectively.
- The studies also confirmed that the following were the risk factors for bone health such as
    - advanced age,
    - advanced disease,
    - severity of disease
    - low BMI
    - Increased cumulative steroid use
    - Oral steroid intake
    - Low fat free mass
    - Low FEV1

These risk predictors for the adverse bone health is not consistent across all studies. In our study there was trend towards poor bone health in in age more than 60 years and low BMI. These predictors are interconnected with demographic profile of the patient studied and also the different treatment modality and concentration of the steroids in these modalities

LIMITATIONS

LIMITATIONS

These are the limitations that we found in our study:

1. A major limitation of our study was a small sample size which prevents us from generalizing the results to all COPD patients. Further the patients were unequally distributed according to the severity of disease (as per GOLD criteria). This makes subgroup analysis according to different stages of COPD difficult.

2. There was no age matched control group for comparasion hence it is difficult to interpret the statistical significance of our results.

3. The study was conducted in a tertiary care hospital where patient profile (in terms of disease severity and comorbid conditions) is different compares to the general population

4. Another limitation was cross-sectional design of the study hence the clinical impact of the results of the study could not be measured.

5. Majority of the subjects included in the current study were South Indian men; hence, the results could be applied only to this population. Various parameters included in this study are liable to get affected by gender, ethnicity as well as food habits.

RECOMMENDATIONS

AND

FUTURE DIRECTIONS

RECOMMENDATION AND FUTURE DIRECTIONS

Given the high prevalence of low bone mass detected in our study group it is without hesitation that we recommend evaluation of all COPD patients for bone health. We also recommend future work in the following areas will benefit the patient care

- To study the osteoporotic risk in the female COPD patients

- Prospectively follow up of COPD patient with osteoporosis atleast for a minimum of 10 years

- Formulation of fracture risk score in COPD patient with osteoporosis

- Inclusion of COPD as a risk factor in the WHO FRAX algorithm

- Randomised controlled trials to study the effect of pulmonary rehabilitation on the bone health in patient with COPD

- An intervention to study the effect of bone medication in the disease outcome in COPD patient with Osteoporosis

CONCLUSIONS

CONCLSUIONS

The aim of the study was achieved:

A. The prevalence of osteoporosis among male patients with chronic obstructive pulmonary disease visiting the tertiary care centre was studied and was found to be 61% (41/67). In simple terms one in two patient with COPD has osteoporosis

B. The factor which showed trends towards adverse bone health in COPD patients were:

   i. Advanced age

   ii. Low body mass index

C. Osteopenia was present in 33% (22/67) of the study population

D. Only 6%(4/67) of the study population had normal values for the bone mineral density

E. The prevalence of metabolic bone abnormality in patient with COPD in this study were

   i. Vitamin D deficiency in 69 %(46/67),

   ii. Hypocalcaemia in 4 %(3/67) and

   iii. Raised alkaline phosphatase and parathormone in 8% (6/67) and 31 %(21/67) respectively.

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APPENDIX

List of annexures included

Annexure I- Patient information and consent form

Annexure II- Data abstraction form

Annexure III- Data sheet

Annexure IV-Standard operation protocol

Annexure I- Patient information and consent form

PARTICIPANT INFORMATION SHEET

Christian Medical College & Hospital, Vellore

You are being invited to participate in a research study. Your participation in this study is entirely voluntary. Your decision whether or not to participate will have no effect on the quality of medical care you will receive in this hospital.

An investigator in this study will explain the purpose of this study including how this study will be carried out and your contribution or role in the study. The paragraphs below explain the study. Please ask questions if there is anything you do not understand before you decide to participate in this study.

STUDY TITLE

BONE HEALTH IN CHRONIC OBSTRUCTIVE AIRWAY DISEASES.

PRINCIPAL INVESTIGATOR: Dr. Mohammad Sadiq.J

What is the purpose of this study?

This study plans to look bone health in male patient with chronic obstructive airway disease. It is well known fact that COPD and its treatment affect the bone health. But there is no Indian study to show how common is this problem in Indian population.

What does this study involve?

The blood samples will be tested for parameters related to bone health. Other tests which includes chest x-ray, lumbo-sacral spine x-ray, DXA scan, 6MWT (six minute walk test) and spirometry which are related to disease will be tested.

Are there any benefits from participating in this study?

These tests will provide an existing bone health of your body. If there is any abnormality detected in any of the test you will be informed if you want to know the results. We will not provide treatment as part of this study and you will be treated in this hospital if you wish to do so as any general medical condition. This study is helpful for science and humanity.

What are the risks involved in participating in this study?

Participating in this study does not affect your health in any adverse manner. You will receive the same standard care regardless of your willingness to participate in the study.

Will my taking part in this study be kept confidential?

All information collected about you during the course of research will be kept strictly confidential. Any information which leaves the hospital/clinic/laboratory will have your name and address removed so that you cannot be recognized from it.

What will happen to the results of the research study?
Results of the research will be published in national/international journals. We are also assuring you that you will not be identified in any report/publication.

If the above information does not provide answers to your questions, request the investigator to answer them for you. Also, this sheet is for your information and you can retain this copy with you.

Contact for further information-
For further information kindly contact-

Dr Mohammad Sadiq.J,
PG Registrar Department of General Medicine
Christian Medical College and Hospital, Vellore -632004,
Tamil Nadu, India.
Ph no: 09443045199
Email: mohammadsadiqj@gmail.com

Thank you for taking part in this research study.

CONSENT FORM

Christian Medical College & Hospital, Vellore.

STUDY TITLE

BONE HEALTH IN CHRONIC OBSTRUCTIVE AIRWAY DISEASES

PRINCIPAL INVESTIGATOR

Dr. Mohammad Sadiq J

A. I _____, understand that the physicians at the department of Medicine, Endocrinology and Pulmonary Medicine, Christian Medical College are engaged in research on the nature, diagnosis and treatment of Diabetes.

B. I have been informed that this study involves research and that the purpose is to assess the bone health in COPD patient

C. I understand that a sample of blood (10ml) will be drawn once for research purposes and not as a routine clinical test, and that this blood sample may be stored and used in the laboratory for many years, in relation to treatment objectives of this study until it is used up. A chest x-ray and DXA scan will also be taken.

D. I understand that the possible discomforts and risks attendant to this procedure include some degree of pain from the insertion of the needle into the vein and radiation exposure, but this is usually minimal. An occasional patient faints due to blood sampling procedure, and rarely there is some discomfort for a few days at the site of venipuncture due to the formation of a bruise. If any tests are performed on my blood, I will be told which tests have been performed and the results could be made available to me.

E. I understand that the records connected with my participation in the clinical investigation will be kept strictly confidential. My name will not be revealed in any publication that may arise from this study.

F. I have had the opportunity to ask questions concerning the procedures to be used. I understand that if I have any further questions concerning the research conducted, I may contact Dr. Mohammad Sadiq. J or his co-investigators in the department Medicine, Endocrinology and Pulmonary medicine, Christian Medical College, and Vellore.

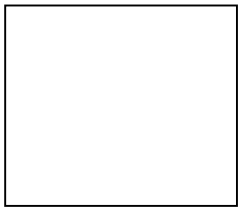
G. I further understand that I am free to withdraw my consent at any time without any penalty or loss of benefits to which I may be otherwise entitled. I also will not be paid for participation in this study but there will be no additional cost to me for evaluations necessary for this study

H. I hereby voluntarily consent to participate in this study and to allow the procedures described above to be performed on me.

_____ _____

Signature of Subject Date

OR



Thumb Impression

INVESTIGATOR'S OR SUB-INVESTIGATORS STATEMENT

I have offered an opportunity for further explanation of this procedure to the individual whose signature appears above.

_____

Note: The subject shall be given a copy of this consent form. A signed copy must be filled in the patient's file at the Department of Endocrinology, Christian Medical College & Hospital,Vellore.

Annexure II- Data abstraction form

SR NO:_____		Date_____	
THE BOAD STUDY			
DEMOGRAPHIC DATA			
Age		Hospital No	
Occupation		Tel No:	
Address:			
HISTORY			
COPD HISTORY			
Duration			
GOLD COPD Stage (Appendix 1)			
BODE severity index(Appendix 2)			
COPD TERATMENT HISTORY			
Inhaled steroids			
Drug			
Dose			
Duration			
Last dose			
Oral steroids			
Drug			
Dose			
Duration			
Last dose			
SMOKING HISTORY			
Pack-years			
Current smoker	Yes/No		
If no stopped smoking since	_____months		
OTHER RELEVANT HISTORY			

Backache	
Duration	**_____years**
Treatment	**Calcium, Vitamin D/ Bisphosphonates**
History of fracture	
Sun-light exposure duration	
History of loss of libido	**Yes/No**
Diabetes	**Yes/No**
Duration	**_____years**
Treatment	**OADS/Insulin/Both**
Hypertension	**Yes/No**
Duration	**_____years**
Treatment	**Yes/No**
Dyslipidemia	**Yes/No**
Treatment	**Yes/No**

DIET AND PHYSICAL ACTIVITY	
Dietary recall	**_____Kcal/day**
Dietary calcium intake	

RELEVANT EXAMINATION	
Weight (Kg)	**Systolic BP (mmHg)**
Height (cm)	**Diastolic BP (mmHg)**
BMI (kg/m2)	
Waist circumference (cm)	
W/H ratio(___cm/___cm)	

SPIROMETRY	
FEV1	
FVC	
FEV1/FVC	
6 MWT	

INVESTIGATIONS	
Calcium	
Phosphorus	
Albumin	
Alkaline phophotase	
25 hydroxy-vitamin D	
Creatinine	
Testosterone	
iPTH	
DXA	
T score	
Femoral Head	
Lumbar spine	

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Appendix 1: GOLD classification of COPD

GOLD Stage	Spirometry
I	FEV_1/FVC <0.7 and FEV_1 80% predicted
II	FEV_1/FVC <0.7 and 50% FEV_1 <80% predicted
III	FEV_1/FVC <0.7 and 30% FEV_1 <50% predicted
IV	FEV_1/FVC <0.7 and FEV_1 <30% predicted or FEV_1 <50% predicted with respiratory failure or signs of right heart failure

Appendix 2: BODE disease severity index

Parameter	0	1	2	3
BMI	>21	≤21	—	—
Obstruction: FEV_1 (% predicted)	≥65%	50–64%	36–49%	≤35%
Dyspnea: MMRC score	0-1	2	3	4
Exercise: 6-minute walk distance (meters)	≥350	250–349	150–249	≤149

Annexure III- Data sheet

S.No.	Name	CMCH	Age	Place	Occupation	Duration of COPD(Months)	GOLD stage	FVC	FEV1	FEV 1/FVC	MMRC	6 mwd distance	BODE Index	Inhaled steroid drug	Inhaled steroid dose/d	daily dose	steroid Duration	total dose	oral steroid drug	oral steroid dose	oral steroid Duration (in the last steroid days from toda	Smoking (pack-years	current smoker	H/o backache	non-fluke backache	V/L fx/ backache	h/o fracture	sunlight exposure(min/day)	dietary calcium intake	D
1	C.k.v. gopi	038923c	58	Tamilnadu	Manual laboure	24	3	44	35	78	2	254.38	9	Budesonide	200	800	12	9600	none	none	none	none	80	no	no	NA	no	no	20	1060	
2	Chakravarthy	349739C	58	Tamilnadu	Manual laboure	180	4	54	22	42	3	267.46	11	Budesonide	400	1600	120	192000	none	none	none	none	Nil	no	no	NA	no	no	20	1180	
3	Chinnappan	231127F	59	Tamilnadu	Manual laboure	12	3	47	30	59	2	253.68	10	Budesonide	200	800	120	96000	none	none	none	none	30	no	yes	24	no	no	10	850	
4	Dhanapal	405945D	60	Tamilnadu	Retired employe	24	4	48	17	39	4	358	11	Budesonide	200	800	24	19200	none	none	none	none	30	no	no	NA	no	no	10	1300	
5	Duraisamy Gounder	014348F	70	Tamilnadu	Retired employe	24	3	51	43	79	2	300.3	9	Budesonide	200	800	24	19200	none	none	none	none	30	no	no	NA	no	no	20	980	
6	H.A. Mallick	312974F	70	Tamilnadu	Retired employe	84	3	76	36	47	2	162.35	11	Budesonide	200	800	12	9600	none	none	none	none	10	no	no	NA	no	no	10	980	
7	Harikrishnan	796079c	69	Tamilnadu	Retired employe	84	4	43	16	42	4	336.3	11	Budesonide	200	800	72	57600	Prednisolone	40 mg	5 days	7 months	50	no	no	NA	no	no	10	1220	
8	Kathavarayan	332120f	55	Tamilnadu	Bussiness	72	2	77	60	83	1	376.32	5	Budesonide	200	800	72	57600	none	none	none	none	30	no	no	NA	no	no	10	900	
9	KB Babu	146073F	60	Tamilnadu	Bussiness	24	4	60	28	49	3	301.29	10	Budesonide	200	800	24	19200	none	none	none	none	80	yes	no	NA	no	no	20	960	
10	Krishnan	178540F	55	Tamilnadu	Bussiness	36	3	48	34	71	2	384.09	9	Budesonide	200	800	432	345600	none	none	none	none	30	no	yes	36	no	no	10	1350	
11	Kuppan Chetty	464560D	70	Tamilnadu	Retired employe	120	3	81	38	60	2	386	8	Budesonide	200	800	60	48000	none	none	none	none	Nil	no	no	NA	no	no	10	1170	
12	Madhavan	222881F	58	Tamilnadu	Retired employe	39	2	83	69	84	1	456.96	5	Budesonide	100	400	3	1200	none	none	none	none	40	no	no	NA	no	no	20	1020	
13	Mani	615686B	60	Tamilnadu	Retired employe	84	4	34	15	48	4	383.88	10	Budesonide	200	800	60	48000	Prednisolone	20 mg	5 days	9 months	10	no	no	NA	no	no	10	1030	
14	Mubarak Ali	801674C	55	Tamilnadu	Bussiness	60	4	50	26	52	3	303.3	11	Budesonide	200	800	24	19200	Prednisolone	40 mg	7 days	8 months	60	no	yes	24	no	no	10	1350	
15	Padmanaban	216363D	62	Tamilnadu	Retired employe	60	1	84	83	96	1	446.4	5	Budesonide	200	800	60	48000	Prednisolone	10 mg	7 days	3 months	60	no	yes	24	no	no	10	950	
16	Palani	710010C	54	Tamilnadu	Bussiness	60	4	49	23	54	3	369.7	9	Budesonide	200	800	24	19200	none	none	none	none	25	yes	yes	24	no	no	20	1180	
17	Perumal	261435F	61	Tamilnadu	Retired employe	120	3	55	35	63	2	456	9	Budesonide	200	800	60	48000	none	none	none	none	Nil	no	no	NA	no	no	> 30	820	
18	Prabhu	275801c	51	Tamilnadu	Bussiness	36	3	58	41	70	2	434.88	8	Budesonide	200	800	24	19200	none	none	none	none	15	no	yes	60	no	no	20	780	
19	Rajareddy	312611F	65	Tamilnadu	Bussiness	36	3	62	35	61	2	382.23	8	Budesonide	200	800	36	28800	Prednisolone	20	5 days	1 month	75	yes	yes	36	no	no	10	1220	
20	Ramanujam	173557f	60	Tamilnadu	Bussiness	12	2	66	54	84	1	318.25	7	Budesonide	200	800	12	9600	none	none	none	none	60	no	no	NA	no	no	10	1000	
21	Ramesh P	762560D	54	Tamilnadu	Manual laboure	180	4	40	20	50	3	287.82	11	Budesonide	200	800	24	19200	none	none	none	none	40	no	yes	24	no	no	10	1000	
22	Satyendra	062475c	64	Tamilnadu	Retired employe	60	4	44	29	66	3	345.6	11	Budesonide	200	800	60	48000	none	none	none	none	30	no	yes	12	no	no	> 30	1120	
23	Sayed Zafrulliah	709672c	52	Tamilnadu	Bussiness	36	2	70	73	106	1	423	5	Budesonide	200	800	24	19200	none	none	none	none	15	no	no	NA	no	no	10	980	
24	sekar	507041b	53	Tamilnadu	Bussiness	6	4	61	26	40	3	275.4	10	Budesonide	200	800	6	4800	Prednisolone	20	14 days	6 months	30	no	yes	60	no	no	10	820	
25	Shanmugam	159476C	68	Tamilnadu	Retired employe	48	3	47	43	90	2	379.44	8	Budesonide	200	800	24	19200	none	none	none	none	15	no	yes	60	no	no	20	860	
26	Sivalingam	943626C	70	Tamilnadu	Bussiness	60	2	82	51	70	1	300.39	6	Budesonide	200	800	60	48000	none	none	none	none	50	yes	yes	36	no	no	10	1180	
27	Subramani	197430D	70	Tamilnadu	Bussiness	72	3	87	46	56	1	366	6	Budesonide	200	800	24	19200	none	none	none	none	Nil	no	no	NA	no	no	10	820	
28	Sundaram	304208F	60	Tamilnadu	Bussiness	24	2	73	67	94	1	485.97	5	Budesonide	200	800	12	9600	none	none	none	none	120	yes	yes	24	no	no	10	1290	
29	Syed Ahmed	348354F	70	Tamilnadu	Bussiness	36	3	63	39	64	2	330.88	8	Budesonide	200	800	432	345600	none	none	none	none	Nil	no	no	NA	no	no	> 30	1230	
30	Thaher	289924F	52	Tamilnadu	Manual laboure	72	2	79	54	71	1	479.4	6	Budesonide	200	800	72	57600	none	none	none	none	15	no	no	NA	no	no	20	1240	
31	Vijayakumar	885009d	50	Tamilnadu	Manual laboure	60	4	49	30	61	3	327.85	11	Budesonide	200	800	60	48000	none	none	none	none	no	no	no	NA	no	no	> 30	1100	
32	Vijendran	200961F	51	Tamilnadu	Bussiness	120	4	40	26	66	3	251	11	Budesonide	200	800	60	48000	none	none	none	none	20	no	no	NA	no	no	> 30	1620	
33	Govindasamy	894069D	60	Tamilnadu	Bussiness	24	4	55	26	51	3	100	12	Budesonide	200	800	24	19200	Prednisolone	20	14 days	3 months	15	no	yes	24	no	no	10	1220	
34	Kannan	955510d	68	Tamilnadu	Retired employe	240	4	32	16	53	4	347.1	11	Budesonide	200	800	24	19200	Prednisolone	20	14 days	6 months	30	no	yes	60	no	no	10	1020	
35	Kesavan	454607D	50	Tamilnadu	Manual laboure	10	3	56	32	59	2	427.2	9	Budesonide	200	800	6	4800	none	none	none	none	40	no	no	NA	no	no	10	1440	
36	Suandar Babu	593665b	58	Tamilnadu	Manual laboure	60	4	69	44	64	2	320.85	9	Budesonide	200	800	60	48000	none	none	none	none	10	yes	no	NA	no	no	20	980	
37	Madan	335639f	61	Tamilnadu	Retired employe	12	2	47	79	55	1	498	4	Budesonide	200	800	12	9600	none	none	none	none	20	yes	no	NA	no	no	20	740	
38	Raja	635159b	70	Tamilnadu	Retired employe	120	2	94	66	72.3	1	307.2	6	Budesonide	200	800	120	96000	prednisolone	40 mg	12 days	2 months	30	no	no	NA	no	no	10	1140	
39	Kumar	621883D	62	Tamilnadu	Retired employe	360	4	49	25	53.2	2	449.28	8	Budesonide	200	800	360	288000	prednisolone	40 mg	12 days	12 months	30	no	no	NA	no	no	10	980	
40	Devandran	839959D	67	Tamilnadu	Retired employe	120	4	47	27	59	2	300	10	Budesonide	200	800	60	48000	none	none	none	none	48	no	no	NA	no	no	20	1300	
41	dhakshnamoorthy	367333f	53	Tamilnadu	Bussiness	60	2	68.2	40.4	63.1	2	288	8	Budesonide	200	800	12	9600	none	none	none	none	30	no	yes	24	no	no	20	880	
42	abdul jabber	449053d	65	Tamilnadu	Retired employe	84	2	57.5	56.3	100.7	3	129	11	Budesonide	200	800	84	67200	Prednisolone	40	8 days	7 months	20	no	yes	60	no	no	10	980	
43	kesavan	275129c	54	Tamilnadu	Bussiness	48	3	62.6	32.9	56.9	2	402.69	8	Budesonide	200	800	24	19200	none	none	ni	none	10	no	yes	36	no	no	20	1200	
44	manikam	247296d	69	Tamilnadu	Retired employe	96	3	60	45	75	4	383.59	10	Budesonide	250	1000	72	72000	none	none	no	none	20	no	yes	12	no	no	20	1080	
45	mariappan	398829f	68	Tamilnadu	Retired employe	12	2	77.4	42.9	57.5	3	371.42	8	Budesonide	250	1000	12	12000	none	none	no	none	20	no	yes	60	no	no	>30	980	
46	arokiasamy	743283f	50	Tamilnadu	Bussiness	120	3	51.7	33.6	65.9	3	388.97	10	Budesonide	250	1000	24	24000	none	none	no	none	20	no	yes	120	nil	no	20	900	
47	stanely	027176f	65	Tamilnadu	Retired employe	60	4	46.5	25.9	58.2	3	479.22	10	Budesonide	200	800	48	38400	none	none	no	none	24	no	yes	24	nil	no	20	940	
48	Chakravarty	331395D	51	Tamilnadu	Bussiness	72	4	46.7	39.5	84.7	2	443.52	8	Budesonide	200	800	72	57600	none	none	none	none	105	no	no	NA	no	no	>30	900	
49	basheer ahamed	652706f	52	Tamilnadu	Manual laboure	72	4	33.2	17.4	55.3	2	308	9	Budesonide	200	800	24	19200	none	none	no	none	10	no	no	NA	no	no	10	900	
50	arumugam	647016f	67	Tamilnadu	Retired employe	48	3	76.2	66.7	91.1	3	232	9	Budesonide	200	800	48	38400	none	none	no	none	100	no	yes	120	no	no	10	1180	
51	md rahaman	864286f	52	Tamilnadu	Manual laboure	24	2	86	77	90	2	324	7	Budesonide	200	800	24	19200	none	none	no	none	28	no	yes	48	no	no	10	1440	
52	Ashok	864512f	51	Tamilnadu	Manual laboure	48	2	77	71	93	1	476.28	5	Budesonide	200	800	4	3200	none	none	no	none	72	no	no	NA	no	no	10	940	
53	Abdul	866582f	52	Tamilnadu	Manual laboure	60	4	48.8	26	54.6	2	368.92	9	Budesonide	200	800	36	28800	none	none	no	none	80	no	yes	84	no	no	10	1460	
54	Ashokan	381139b	57	Tamilnadu	Bussiness	60	4	44	23	53	2	464.63	9	Budesonide	250	1000	60	60000	none	none	no	none	20	no	no	NA	no	no	20	2080	
55	Vinayagam	383974D	67	Tamilnadu	Retired employe	72	3	46.8	44.1	86.5	3	297	10	Budesonide	200	800	72	57600	none	none	no	none	28	no	yes	48	no	no	10	1420	
56	Ramesh	865293f	61	Tamilnadu	Bussiness	12	3	47.8	40.1	83.1	3	242	11	Budesonide	200	800	12	9600	none	none	no	none	5	no	yes	48	no	no	10	1400	
57	subramani	835481D	70	Tamilnadu	Bussiness	48	3	79.5	39.2	53.4	4	102	12	Budesonide	200	800	48	38400	none	none	no	none	30	no	yes	48	no	no	>30	1100	
58	Arjunan	070609f	52	Tamilnadu	Manual laboure	36	3	38.1	40.8	75.2	1	490.49	6	Budesonide	200	800	36	28800	Prednisolone	40	7 days	3 months	15	no	yes	24	no	no	10	940	
59	devarajan	533298A	55	Tamilnadu	Bussiness	12	2	80.7	65.3	83.4	2	301.15	7	Budesonide	200	800	12	9600	none	none	no	none	12	no	no	NA	no	no	10	1640	
60	gopal	910519f	70	Tamilnadu	Retired employe	2	2	73.8	67	95	3	320	7	Budesonide	200	800	2	1600	none	none	no	nine	45	no	yes	84	no	no	10	1420	
61	sharfuddin	868862d	61	Tamilnadu	Retired employe	48	4	76.3	30.6	43.5	2	243.66	10	Budesonide	200	800	24	19200	Prednisolone	40	7 days	1 month	36	no	yes	48	no	no	10	1080	
62	Duraisamy	690537F	65	Tamilnadu	Bussiness	24	3	89.3	95.2	104.8	3	449.11	7	Budesonide	400	1600	24	38400	none	none	no	none	72	no	no	NA	no	no	10	1510	
63	Purushothaman	683474F	55	Tamilnadu	Bussiness	8	3	58.3	40.2	73.5	1	426.8	6	Budesonide	400	1600	8	12800	none	none	no	none	36	no	yes	72	no	no	10	1390	
64	Perumal	219876f	52	Tamilnadu	Manual laboure	36	2	87.6	58	69.2	1	469.98	5	Budesonide	400	1600	36	57600	Prednisolone	40	7 days	4 months	36	no	yes	72	no	no	20	1600	
65	Kuppaiah	709588f	64	Tamilnadu	Retired employe	24	3	66.1	66.1	99.4	2	352.8	6	Budesonide	400	1600	24	38400	Prednisolone	40	7 days	6 months	36	no	yes	48	no	no	10	1620	
66	Annamalai	089478f	70	Tamilnadu	Retired employe	48	3	114.1	54.1	50	3	356.72	7	Budesonide	200	800	48	38400	none	none	no	none	44	no	no	NA	no	no	10	1420	
67	Subramani	006513d	67	Tamilnadu	Bussiness	72	2	63.9	33.2	56.4	2	268	9	Budesonide	200	800	72	57600	none	none	no	none	42	no	no	NA	no	no	>30	1690	

Loss of libido	diabetes	hypertension/Treatment for hypertension	Anemia/Treatement for dyslipidemia	Pulse	Sys_BP	Dia_BP	Height	Weight	BMI	Waist	Hip	WtHR	PTH	albumin	vit_D	ca	phosp	alk.phos	testo	creat	Hbalc	f_arm_bmd	f_arm_T	f_arm_Z	LS_BMD	LS_T	LS_Z	neck_bmd	neck_T	neck_Z	hip_BMD	hip_T	hip_Z
no	yes	yes	no	102	130	90	162	49	18.67	82	80	102.50	100.6	4.7	13.39	9.3	3.6	75	229	1.05	6.3	0.601	-1.7	-0.9	0.805	-2.6	-2	0.502	-3.1	-2.2	0.69	-2.3	-1.8
no	no	no	no	102	142	80	168	75	26.57	103	101	101.98	50.4	4	23.62	8.8	3.5	65	203	1.01	5.9	0.759	1.4	2.1	0.922	-1.5	-0.9	0.776	-1.1	-0.2	0.475	-2.2	-0.6
no	no	no	no	90	130	100	168	105	37.20	129	133	96.99	112	4.1	24.2	9.3	4.2	100	444	1.14	6.2	0.732	0.9	1.6	1.299	1.9	2.5	1.069	1	1.9	1.318	1.9	2.3
no	no	no	no	92	90	68	151	60	26.31	92	90	102.22	44.2	4.3	24.55	9.3	4.1	85	498	1.24	8.2	0.611	-1.5	-1	1.043	-0.4	-0.1	0.737	-1.4	-0.7	37.66	-0.2	0.1
no	no	no	no	100	122	82	150	66	29.33	106	101	104.95	59.7	4.1	9.9	9.3	4.6	95	338	1.11	5.8	0.611	-1.5	-0.2	1.057	-0.3	0.6	0.799	-1	0.2	1.02	-0.1	0.6
no	no	no	no	90	122	80	167.5	77	27.44	104	102	101.96	117.3	3.5	6.24	8.9	2.7	97	206	1.18	6.3	0.49	-3.8	-2.5	0.916	-1.6	-0.7	0.541	-2.9	-1.7	0.76	-1.8	-1.1
no	no	no	no	92	130	90	163	41	15.43	75	77	97.40	59.5	3.9	8.38	9.6	3	104	591	1.1	6	0.478	-4	-2.8	0.788	-2.8	-1.9	0.488	-3.2	-2.1	0.606	-2.8	-2.2
no	Yes	Yes	no	88	140	80	151	45	19.74	76	80	95.00	23.2	4.8	>70	10	3.6	63	137	0.87	7.9	0.647	-0.8	-0.4	0.859	-2.1	-1.8	0.715	-1.6	-0.9	0.906	-0.8	-0.5
no	no	no	no	76	110	66	170.5	53	18.23	83	85	97.65	11.3	4.7	62.95	9.6	3.5	109	537	1.13	5.9	0.557	-2.5	-1.2	1.107	0.1	1.1	0.637	-2.2	-0.9	0.385	-2.8	-0.9
no	no	yes	no	84	120	80	158.5	80	31.84	106	102	103.92	46.3	4.4	7.31	9.6	3.8	105	122	1.3	6.9	0.608	-1.5	-0.9	0.664	-3.9	-3.4	0.573	-2.6	-1.8	0.904	-0.9	-0.5
no	no	no	no	97	145	80	162.5	60	22.72	90	90	100.00	95.2	4.2	18.2	9	2.6	59	303	1.26	5.7	0.667	-0.4	0.8	0.988	-0.9	-0.1	0.715	-1.6	-0.4	0.887	-1	-0.3
no	no	no	no	68	124	90	165	69	25.34	88	94	93.62	67.7	4.4	25.48	8.9	3.4	36	368	1.11	6.7	0.678	-0.2	0.5	1.05	-0.2	0.3	0.941	0.1	1	1.172	0.9	1.3
yes	yes	no	no	108	94	70	159	45	17.80	80	82	97.56	38.1	4.5	34.53	9.8	4.1	46	394	0.9	7	0.69	0.1	0.8	0.876	-2	-1.3	0.712	-1.6	-0.6	0.96	-0.5	0
no	no	no	no	99	112	70	156.5	63	25.72	89	89	100.00	47.9	4.1	21.46	8.3	3.6	123	219	1.18	7	0.679	-0.1	0.4	0.896	-1.8	-1.3	0.572	-2.6	-1.8	0.777	-1.7	-1.3
no	no	no	no	74	120	90	164	85	31.60	103	106	97.17	37.1	4.6	17.47	9.7	3.8	88	306	0.8	6.9	0.457	-1.5	-0.5	1.123	0.3	1	0.761	-1.2	-0.3	0.951	-0.5	-0.1
no	no	no	no	85	120	90	155.3	33	13.68	63	70	90.00	64.2	4.1	18.2	9.1	4.6	57	461	1.18	5.9	0.457	-4.4	-3.9	0.588	-4.6	-4.1	0.386	-4	-3.1	0.495	-3.6	-3.2
no	no	no	no	92	116	70	160	64	25.00	96	92	104.35	96.4	4.6	10.07	9.1	2.8	61	401	1.26	5.8	0.597	-1.7	-0.9	0.836	-2.3	-1.7	0.645	-2.1	-1.1	0.883	-1	-0.5
yes	no	yes	yes	85	140	100	160	60	23.44	88	92	95.65	36	3.8	20.85	9.1	3.7	110	665	1.02	6.6	0.657	-0.6	-0.2	1.068	-0.2	0.1	0.763	-1.2	-0.5	0.876	-1	-0.7
no	no	no	no	75	126	74	173	51	17.04	73	81	90.12	81.4	4.4	52.55	9.2	4.5	73	702	0.9	5.8	0.561	-2.4	-1.4	0.765	-3	-2.2	0.644	-2.1	-1	0.763	-1.8	-1.3
no	yes	yes	yes	92	140	90	143	45	22.01	90	94	95.74	46	3.8	34.29	9.1	3.1	183	76.8	1.54	7.1	0.498	-3.6	-2.8	0.868	-2	-1.4	0.607	-2.4	-1.4	0.736	-2	-1.5
no	no	no	no	90	130	90	163	63	23.71	98	101	97.03	27.5	4.1	30.59	9.1	5.4	78	448	0.99	6.5	0.528	-3.1	-2.5	0.868	-2	-1.6	0.714	-1.6	-0.8	0.9	-0.9	-0.5
no	no	no	no	75	150	80	159	60	23.73	89	90	98.89	76.1	4.1	17.96	8.6	2.7	89	396	1.39	5.7	0.53	-3	-2.1	0.784	-2.8	-2.1	0.49	-3.2	-2.2	0.723	-2.1	-1.6
no	yes	yes	no	105	144	88	167	92	32.99	116	106	109.43	53.7	4.8	10.21	9.4	4.2	88	219	1.16	8.1	0.619	-1.3	-0.8	0.847	-2.2	-1.8	0.699	-1.7	-0.9	0.804	-1.5	-1.2
no	yes	yes	no	111	126	80	159	50	19.78	80	82	97.56	75.4	4.7	20.83	9.4	3.5	50	337	1	6.8	0.722	0.7	1.2	1.018	-0.7	-0.2	0.861	-0.5	0.3	1.122	0.6	0.9
yes	no	yes	yes	86	128	60	162	70	26.67	94	100	94.00	20.4	4.1	23.89	9	3.9	62	317	1.6	9	0.598	-1.7	-0.6	0.896	-1.8	-0.9	0.752	-1.3	-0.2	0.917	-0.8	-0.2
no	no	no	no	80	130	90	168	37	13.11	72	75	96.00	30.3	4.2	40.7	9	3.4	69	487	1.16	5.5	0.408	-5.4	-4.1	1.068	-0.2	0.7	0.632	-2.2	-1	0.719	-2.1	-0.9
no	no	no	no	92	100	69	163	50	18.82	83	87	95.40	58	4.4	28.21	9.3	3.7	74	503	1.43	5.9	0.533	-3	-1.7	0.814	-2.5	-1.6	0.504	-3.1	-1.9	0.724	-2	-1.4
no	yes	no	no	62	138	88	167	62	22.23	94	90	104.44	65.4	4.4	47.62	10.3	2.1	88	515	1.16	6.6	0.631	-1.1	-0.3	1.083	-0.1	0.6	0.679	-1.8	-0.9	0.398	-2.7	-1.1
no	no	no	no	104	150	74	162	54	20.58	86	85	101.18	50.1	4.2	12.7	9.3	3.9	124	370	1.06	5.3	0.547	-2.7	1.3	0.782	-2.8	-1.8	0.541	-2.9	-1.6	0.745	-1.9	-1.2
no	no	no	no	92	120	80	158	60	24.03	98	101	97.03	20.5	4.7	30.46	9.2	3.3	68	654	1.31	6.4	0.459	-1.5	-0.9	0.976	-1	-0.8	0.636	-2.2	-1.5	0.878	-1	-0.7
no	no	no	no	106	110	92	168	67.4	23.88	96	90	106.67	94.6	5.2	19.13	9.7	3.5	95	373	1	7.9	0.669	-0.3	0	0.914	-1.6	-1.4	0.949	0.1	0.7	1.086	0.4	0.6
no	no	no	no	72	108	64	173	96	32.08	111	108	102.78	46.4	3.4	15.17	9	2.4	62	266	1.07	6.8	0.569	-2.3	-1.8	0.838	-2.3	-1.9	0.618	-2.3	-1.5	0.813	-1.5	-1.1
no	no	no	no	66	148	100	152	37	16.01	67	71	94.37	57.5	4.6	36.19	9.6	4.1	75	279	1.06	5.9	0.442	-4.7	-3.9	0.609	-4.4	-3.7	0.476	-3.3	-2.4	0.663	-2.5	-2
no	yes	yes	no	111	126	80	159	50	19.78	80	82	97.56	34.4	4.1	22.45	10.3	3	126	186	0.75	7.2	0.517	-3.3	-2.2	0.94	-1.4	-0.6	0.642	-2.1	-1	0.832	-1.3	-0.8
no	no	no	no	82	160	100	164	67	24.91	103	106	97.17	85.8	4.4	8.98	9.4	4.8	65	825	1.17	6.5	0.431	-1.9	-1.5	0.696	-3.6	-3.4	0.573	-2.6	-2	0.821	-1.4	-1.1
yes	yes	no	no	84	134	90	172	72	24.34	101	104	97.12	107.4	3.8	4.37	9.3	4.7	52	156	1.21	11.1	0.594	-1.8	-1.1	1.044	-0.4	0.1	0.745	-1.4	-0.5	0.864	-1.1	-0.7
no	no	no	no	88	130	80	165	56	20.57	83	89	93.26	47.9	4.1	33.48	9.5	2.1	92	316	0.9	5.2	0.524	-3.1	-2.3	0.734	-3.2	-2.6	0.682	-1.8	-0.8	0.945	-0.6	-0.1
no	no	no	no	81	120	82	172	70	23.66	92	89	103.37	99.4	4.2	36.11	9	3.3	89	578	1.33	5.3	0.483	-3.9	-2.7	0.887	-1.9	-1	0.72	-1.5	-0.3	0.97	-0.4	0.2
no	yes	no	no	84	130	90	170	60	20.76	90	83	108.43	61.8	4.8	14.11	9.5	3.3	116	263	1.2	6.7	0.641	-0.9	-0.1	0.92	-1.6	-1	0.816	-0.8	0.1	0.63	-1.1	0.5
no	no	no	no	76	136	72	166	59	21.41	86	86	100.00	23.8	4	22.58	9.6	5	81	498	1.49	6.3	0.492	-3.8	-2.7	0.862	-2.1	-1.3	0.594	-2.5	-1.4	0.849	-1.2	-0.6
no	no	no	no	110	130	90	164	51	18.96	85	84	101.19	57	4.7	14.38	9.6	4.3	53	289	0.59	5.5	0.493	-3.7	-3.2	0.708	-3.5	-3.1	0.56	-2.7	-1.9	0.664	-2.4	-2.1
yes	yes	yes	no	88	160	96	172	68	22.99	90	87	103.45	125.4	4.5	31.99	9.7	3.6	113	84.1	1.13	6.1	0.722	0.7	1.6	0.933	1.4	-0.7	0.701	-1.7	-0.7	0.814	-1.5	-0.9
yes	no	no	no	80	108	78	163	46.16	17.37	80	82	97.56	65	4.2	28.38	9.3	4.4	92	696	0.96	5.6	0.518	-3.3	-2.7	0.821	-2.5	-2	0.648	-2.1	-1.2	0.712	-2.1	-1.8
no	no	yes	yes	84	120	80	168	72	25.51	96	95	101.05	17	4.1	22.54	9.5	4.1	74	56.9	1.18	6.5	0.589	-1.9	-0.6	0.689	-1.8	-0.6	0.817	-1.4	-0.7	0.817	-1.4	-0.7
yes	yes	yes	no	81	116	80	171	59.8	20.45	85	82	103.66	45.4	4.5	37.02	8.7	2.9	63	556	0.72	5.5	0.674	-0.2	0.8	1.112	0.2	1	0.818	-0.8	0.3	0.913	-0.8	-0.2
no	yes	yes	yes	72	110	70	160	69	26.95	93	90	103.33	62.8	4.9	26.49	9.5	4	93	364	0.99	5.6	0.605	-1.6	-1.2	0.93	-1.5	-1.1	0.826	-0.8	0	0.895	-0.9	-0.6
no	no	no	no	84	120	80	163	61	22.96	98	91	107.69	34.8	4.7	24.72	9.9	3.8	79	245	0.85	7.2	0.531	-3	-2	0.856	-2.1	-1.4	0.568	-2.7	-1.6	0.661	-2.5	-2
yes	no	no	no	80	160	80	159	69	27.29	91	89	102.25	24.8	5.1	29.12	10.1	4.3	110	322	1.05	6.5	0.673	-0.3	-0.1	0.851	-2.2	-2.1	0.853	-0.6	-0.1	0.968	-0.4	-0.3
yes	no	no	yes	72	140	70	166	55	19.96	85	85	100.00	40.2	3.5	12	9.5	4	116	426	1.02	6.4	0.677	-0.2	0.1	0.923	-1.5	-1.3	0.707	-1.6	-1	0.785	-1.6	-1.4
no	no	no	no	70	140	70	171	64	21.89	92	90	102.22	54	3.6	4	9.4	2.4	124	142	1.06	6..2	0.732	0.9	1.9	1.122	0.3	1.1	0.949	0.1	1.2	0.986	-0.3	0.3
yes	no	no	yes	76	116	80	166	67	24.31	78	89	87.64	34	3.7	18.05	10.2	3.2	88	420	0.81	5.4	0.695	0.2	0.3	1.13	0.4	0.4	0.858	-0.5	-0.3	1.019	-0.1	0
no	yes	no	yes	84	120	80	169	78	27.31	103	104	99.04	52	4.2	6.7	9.6	3.8	75	540	0.73	6.1	0.594	-1.8	-1.6	0.83	-2.4	-2.3	0.81	-0.9	-0.4	0.928	-0.7	-0.5
yes	yes	yes	yes	70	130	80	162	67	25.53	41	31	132.26	100.4	4	17.97	9.3	3.6	136	340	0.94	6.2	0.695	0.2	0.7	0.872	-2	-1.6	0.812	-0.9	-0.1	0.978	-0.4	0
yes	no	no	no	110	100	70	169	70	24.51	91	98	92.86	35.6	4.4	18.25	9.54	3.2	74	338	0.76	10.3	0.636	-1	-0.5	1.037	-0.5	-0.1	0.759	-1.3	-0.5	0.974	-0.4	-0.1
yes	no	no	no	84	120	80	152	84	36.36	111	101	109.90	142	4.6	8.81	9.49	4	63	207	1.32	5.4	0.622	-1.2	-0.3	1.183	0.8	1.6	0.82	-0.8	0.2	0.993	-0.3	0.2
no	no	no	no	100	130	90	154	61	25.72	90	96	93.75	62	4.3	14	9.53	3	72	433	1.14	5.8	0.619	-1.3	-0.5	0.929	-1.5	-0.8	0.69	-1.8	-0.8	0.871	-1.1	-0.6
no	no	no	no	90	130	80	167	48	17.21	73	80	91.25	22.3	4.5	31.06	9.5	3.2	86	655	0.8	5.8	0.733	-1.6	-0.2	0.824	-2.4	-1.5	0.655	-2	-0.8	0.766	-1.8	-1.1
yes	no	no	no	84	120	80	152	42	18.18	70	78	89.74	124	4.1	18.4	9.2	4	50	573	1.07	5.2	0.613	-1.4	-1.1	0.828	-2.4	-2.1	0.628	-2.2	-1.6	0.774	-1.7	-1.4
yes	no	yes	no	80	120	84	162	59	22.48	85	83	102.41	67.2	4.4	24.86	8.9	4	67	402	0.79	5.3	0.64	-0.9	-0.4	0.94	-1.4	-0.9	0.551	-2.8	-1.9	0.741	-1.9	-1.6
no	no	no	no	78	100	60	164	53.14	19.76	82	88	93.18	148	3.1	5.4	7.6	1.8	63	428	1.44	6.4	0.589	-1.9	-0.6	1.183	0.8	1.7	0.754	-1.3	-0.1	0.942	-0.6	0.1
no	no	no	no	130	120	80	168	46	16.30	71	77	92.21	116	4.1	8.6	9.3	2.8	88	240	1.22	6.4	0.467	-4.2	-3.4	0.72	-3.4	-2.7	0.593	-2.5	-1.5	0.735	-2	-1.5
no	no	no	yes	90	130	90	166	78	28.31	89	102	87.25	82	4.2	14.6	9.8	3.2	146	305	0.95	6.1	0.564	-2.4	-1.3	0.986	-1	-0.2	0.702	-1.7	-0.6	0.96	-0.5	0.1
yes	no	no	no	80	120	20	170	54	18.69	74	87	85.06	45.8	4.5	7.46	9.28	3.5	71	449	0.92	5.6	0.538	-2.9	-2.3	0.886	-1.9	-1.4	0.685	-1.8	-0.9	0.786	-1.6	-1.2
no	no	no	no	84	120	84	176	64	20.66	78	84	92.86	17.1	3.9	36.28	8.9	3.5	92	430	0.87	5.2	0.628	-1.1	-0.8	0.892	-1.8	-1.5	0.831	-0.7	0	0.823	-1.4	-1.1
yes	no	no	no	92	100	70	162	73	27.82	102	97	105.15	101.2	3.9	9.97	8.9	2.7	196	685	1.13	7	0.535	-2.9	-1.5	0.818	-2.5	-1.5	0.675	-1.9	-0.6	0.803	-1.5	-0.8
yes	no	no	no	76	120	80	159	47	18.59	75	84	89.29	98	3.6	12.4	9.7	2.6	128	126	1.32	5.8	0.688	0	2.2	0.954	-1.2	0	0.737	-1.4	0.3	0.876	-1	0.2
yes	no	no	no	80	120	80	158	42	16.82	69	77	89.61	40.2	3.4	40.74	7.89	3	85	332	0.52	4.7	0.384	-5.8	-4.7	0.679	-3.7	-2.9	0.512	-3.1	-2	0.656	-2.5	-1.9

Annexure IV-Standard operation protocol

Standard operation protocol: GOLD classification of COPD	
GOLD Stage	**Spirometry**
I	FEV_1/FVC <0.7 and FEV_1 80% predicted
II	FEV_1/FVC <0.7 and 50% FEV_1 <80% predicted
III	FEV_1/FVC <0.7 and 30% FEV_1 <50% predicted
IV	FEV_1/FVC <0.7 and FEV_1 <30% predicted or FEV_1 <50% predicted with respiratory failure or signs of right heart failure

Standard operation protocol 2: BODE disease severity index

Parameter	0	1	2	3
BMI	>21	≤21	—	—
Obstruction: FEV_1 (% predicted)	≥65%	50–64%	36–49%	≤35%
Dyspnea: MMRC score	0-1	2	3	4
Exercise: 6-minute walk distance (meters)	≥350	250–349	150–249	≤149