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# Study of Bone Mineral Density, Vitamin-D and Body Mass Index in Asthmatic ACOS and COPD Cases: Those who are on Prolonged (more than 3 Years) use of Inhaled Corticosteroids

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## ABSTRACT

***Introduction:*** *Inhaled corticosteroids are the prime choice of treatment for Asthma, ACOS, and COPD cases, but using inhaled corticosteroids with the influencing factors for a longer duration may cause cachexia, skeletal muscle abnormalities, and metabolic syndromes.* ***Objectives:*** *To determine whether the use of inhaled corticosteroids has a harmful effect on bone, in case of Asthma, ACOS, and COPD. To assess the correlation between low bone mineral density with low vitamin D levels and low body mass index. To assess the fracture risk with the effect of inhaled corticosteroids in asthma, ACOS and COPD cases.* ***Methods:*** *A total of 260 subjects (123 males and 137 females) aged ≥ 25 years attended the routine check-up for NRI Institute of Medical Sciences, Visakhapatnam. The pulmonology department was grouped into 4. Data was collected and filed by using data collection sheet, measured bone mineral density with the ultra-sonogram machine, did investigative procedures to know the blood calcium and vitamin-D levels.* ***Results:*** *Our study revealed that all quantitative and qualitative parameters were measured and analyzed with the SPSS software version 18, (vitamin-D, bone mineral density, body mass index, allergies, family, smoking histories and others) obtained a statistically significant p-value.* ***Conclusion:*** *Effect of disease and inhaled corticosteroids use respiratory diseases for a longer duration or in high doses resulting in decreased bone mineral density along with the decreased body mass index.*

**Keywords:** Asthma, ACOS, COPD, Inhaled corticosteroids, Vitamin-D, Bone mineral density

## INTRODUCTION

According to the National Heart, Lung and Blood Institute, asthma is a chronic lung disease, triggered by air pollution, allergens, exercise, infections, emotional/upset or with different foods like dairy products, etc. Typical asthma symptoms include coughing, wheezing, tightness in the chest, difficulty breathing, rapid heart rate, and sweating. Children with asthma often complain of an itchy upper respiratory tract or a dry cough. Asthma is a chronic inflammatory condition that affects both adults and children [1].

Asthma itself does not cause much threat to bone health. Treatments in the form of steroids or inhaled corticosteroids are frequently used to decrease inflammation and airway blockage. The inhaled corticosteroids are considered as the gold standard first-line preventive therapy and are widely recommended in national and international guidelines [2,3]. Though the positive effect on the lungs, it may affect bone health and results in the risk of osteoporosis at an early age.

Chronic obstructive pulmonary disease (COPD) is a major global health concern causing morbidity and mortality around the world. Although it is defined as the presence of chronic airflow limitation, COPD is nowadays considered a complex heterogeneous and multicomponent condition [4]. In addition to COPD other chronic conditions like cardiovascular diseases, depression, osteoporosis, anemia, and diabetes substantially contribute to the severity of the disease [5]. Comorbidities not only affect the symptom burden, but also decrease the functional performance and health status in patients with COPD [6], but also the risk of hospitalization and mortality [7,8].

Orie, et al., during the first Bronchitis Symposium held in Groningen, the Netherlands, hypothesized that the various forms of airway obstruction, such as asthma, chronic bronchitis, and emphysema, should be considered not as separate diseases but as different expressions of one disease entity, which they named chronic non-specific lung disease [9]. Again in 1969, this hypothesis was supported by the Dutch hypothesis.

Duch hypothesis is in contrast to the British hypothesis, where asthma and chronic obstructive pulmonary disease (COPD) are seen as distinct entities generated by different mechanisms [10].

But in recent years, it became clear that some patients are having the clinical feature of both asthma and COPD. The presentation of such clinical features could be another phenotype of the disease called asthma-overlapped by Obstructive Lung Disease known as ACOS [11].

Spanish Respiratory Society proposed diagnostic criteria for ACOS in 2012. Diagnosis is confirmed when 2 major and 2 minor criteria are met (Table 1) [12].

**Table 1 Criteria proposed by spanish respiratory society for acos diagnosis**

| Major criteria | Minor criteria |
|---|---|
| Increase in FEV(1)≥15% and≥400 ml | High total IgE >100 UI/ml |
| Eosinophilia in sputum>5% | Personal history of atopy |
| Personal history of asthma | Increase in FEV(1)≥12% and≥200 ml on 2 or more occasions |

However, globally consensus is still lacking on the existence of ACOS as a separate syndrome, and on its diagnostic criteria [13].

According to GOLD/GINA recommendations normal FEV1/FVC pre or post broncho dilatator test is not compatible with ACOS unless there is other evidence of chronic airflow limitation. FEV1 more or equal to 80% predicted is compatible with the diagnosis of a mild form of ACOS.

FEV1 less than 80% are an indicator of severity and possible complications in the future. Post broncho dilatator increase in FEV1 more or equal to 12% and 200 ml from baseline is common in ACOS if FEV1 is low. Moreover, an increase in FEV1 more than 15% and 400 ml is also compatible with ACOS diagnosis [14].

Other methods such as the assessment of fractional exhaled nitric oxide (FENO) and immunoglobulin E (IgE) in COPD patients were also used in the diagnosis of ACOS. When the cutoff value of FENO was 35 ppb the prevalence rate of ACOS was 16.3% in the COPD group.

But if both FENO and IgE were assessed, the high-FENO/high-IgE group was 7.8% among patients with COPD. This indicates both asthma-like airway inflammation and the presence of atopy in COPD patients [15].

Future studies may demonstrate other markers and criteria for diagnosing ACOS. A recent study demonstrates that inflammatory cytokines IL-4, IL-8, IL-10, and TNF-α are different among control, asthma, COPD with exacerbation and ACOS groups and might be useful in assessing the development of these diseases [16].

The frequency of attacks is more in this group compared with COPD and less when compared with asthma, so overall expenditure for patients is also more in ACOS when compared with the COPD [17].

## MATERIALS AND METHODS

A total of 260 subjects (126 males and 134 females) attending our institutional hospital from 27$^{th}$ December 2017 to 15$^{th}$ March 2019 was included in this study. The study protocol was approved by the institutional ethics committee. Informed consent was obtained from all participants in this study.

While attending the institutional pulmonology department, information like age, sex duration of the severity of disease and details of medications using all details were collected taking a case history and noted on the data collection sheets.

Diagnosis of asthma was done according to the guidelines of (GINA) Global Initiative for asthma. Diagnosis of COPD was done by Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.

### Spirometry Test (PFTs)

Detection of asthma, ACOS, and COPD was confirmed with the presence of a physician, which included forced vital capacity (FVC), Forced expiratory volume in 1 s (FEV1), (FEV1/FVC) and peak expiratory flow rate (PEFR) were done for all patients. Normal values: FEV1/FVC ≥ 70%, abnormal values: mild: 60-69%, moderate: 50-59%, severe: less than 50%.

**Normal Bone Mineral Density Test**

According to WHO, the bone mineral density of the calcaneus was measured by ultrasound densitometry (QUS-2 Calcaneal Ultra sonometer; Hanson Medical Systems, Inc., Orlando, FL) and was expressed as a T-score. T-score <1 is normal, T-scores between -1 and -2.5 were defined as osteopenia, and T-scores <-2.5 were defined as osteoporosis.

**Normal Vitamin D Levels**

Blood samples were collected, centrifuged within 2 h of sampling, and the serum was frozen and stored at -40°C until analyzed for measurement of serum 25-hydroxyvitamin D (25-OHD) by enzyme immune-assay kits supplied by immunodiagnostic AG, Germany.

This kit is a comprehensive protein binding assay for the measurement of 25-OH vitamin D. It is based on competition of 25-OH vitamin D present in the sample competes with the tracer, for the binding pocket of vitamin D binding protein (VDBP) *in vivo*, samples have to be precipitated with precipitation reagent to extract the analyte.

25-OH Vitamin D present in the sample competes with the tracer, coated on the well for the specific binding site of the binding protein and the VDBP is achieved by incubation with a host-specific peroxidase-labeled antibody using TMB (tetramethylbenzidine) as enzyme substrate.

An acidic stopping solution is then added to stop the reaction. The color converts to yellow. The intensity of the yellow color is indirectly proportional to the concentration of 25-OH Vitamin D in the sample.

According to the Endocrine Society Clinical Practice Guidelines, vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level >20 ng/dl, <20 ng/dl is considered as a deficiency, <12 ng/dl is considered as severe deficiency and a level of 30 ng/dl or greater (>75 nmol per liter).

**Normal Serum Calcium Levels**

Normal serum calcium level was 8.5-10.2 mg/dl.

**Normal Body Mass Index**

BMI was calculated by dividing the weight in kilograms by height in meters squared. BMI range between 18.5 and 24.9 is healthy. The 25-29.9 is overweight. Below 18.5 is considered as a deficiency.

Study groups were divided into four groups:

**Group 1:** 65 normal cases were considered as controls

**Group 2:** 65 asthma cases

**Group 3:** 65 ACOS

**Group 4:** 65 COPD cases

**Inclusion Criteria**

Subjects those who were having restlessness, breathing problems, chest tightness, allergies, getting a cough with sputum and those who were on inhaled corticosteroids for 3 years. All the people who participated in this study were having good exposure to sunlight, physical activity, and poor people.

**Exclusion Criteria**

Age below 20 years and above 60 years, those who were not using inhaled corticosteroids with oral corticosteroids, those who were taking dietary supplements, having any other hormonal imbalances, cardiovascular diseases, TB, AIDS, and cancerous situations.

**Statistical Methodology**

Discrete variables were analyzed with Chi-square test and presented as percentages. Continuous variables were analyzed by ANOVA and presented as means ± SD. Relationships between the variables were assessed with the Kruskal-Wallis Test. A p-value of 0.05 was considered significant. All statistical analyses were performed using SPSS version 16.0.

## RESULTS

A total of 260 patients were included in the study and were divided into 4 groups. Both the qualitative and quantitative variables got significant p-values. Each group means and standard deviations of sex, age, bone mineral density, vitamin-D, calcium, and body mass index and other variables are displayed in Table 2.

**Table 2 Showing all measurable means and standard deviations and non-measurable variable percentages**

| Groups | Age | Sex | BMD | Vit-D | Calcium | BMI | BP and diabetes | Smokers | History of fracture | Family history | Allergies |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group 1 | 44.77 | 61.50% | 0.448 | 31.150 | 9.3550 | 31.580 | 83.1% | 83.1% | 93.8% | 26.2% | 23.1% |
| | 13.318 | 38.50% | 0.948 | 8.950 | 7.5710 | 9.840 | | | | | |
| Group 2 | 39.29 | 52.30% | -1.832 | 22.900 | 9.2750 | 26.480 | 67.7% | 64.6% | 83.1% | 60.0% | 52.3% |
| | 2.41 | 47.70% | 4.039 | 10.590 | 0.6352 | 10.320 | | | | | |
| Group 3 | 39.6 | 50.80% | -2.223 | 16.450 | 9.4740 | 24.750 | 75.4% | 72.3% | 86.2% | 55.4% | 53.8% |
| | 11.913 | 49.20% | 0.9219 | 5.744 | 0.6449 | 11.820 | | | | | |
| Group 4 | 50.18 | 24.60% | -2.068 | 17.155 | 9.1260 | 14.180 | 55.4% | 36.9% | 75.4% | 56.9% | 46.2% |
| | 10.904 | 75.40% | 0.8723 | 6.009 | 0.5599 | 3.780 | | | | | |
| Total | 43.46 | 47.30% | -1.419 | 21.880 | 9.3080 | 24.250 | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| | 12.89 | 52.70% | 1.386 | 9.990 | 0.6615 | 11.155 | | | | | |

Among the total cases, 97% comes under the decreased amount of bone mineral density levels, 64.5% deficiency levels with vitamin D. The risk of fracture is with asthma, when we compare with the control group next to asthma the ACOS and COPD groups, because of lowered bone mineral density and vitamin D values.

## DISCUSSION

The mechanism of bone loss induced by glucocorticoids is two-fold, with decreased bone formation and increased bone resorption [17]. Similar findings were observed by Bhattacharya, et al., Canalis, et al., in Indian COPD cases. They studied cases with more severe COPD, had higher risk fractures were comparable between users and non-users of inhaled corticosteroids.

Torch study investigated the long-term effects of therapy with inhaled steroids on BMD and bone fractures in patients with moderate-to-severe COPD [18]. The results of this study met the primary objectives of the study; the effect of inhaled corticosteroids on bone is proved in case of prolonged use in asthma, ACOS and COPD cases.

We observed the other co-factors like smoking, family history and history of fracture in comparison with the normal group. Comparison with the groups of previous studies with the present study is shown in Table 3.

**Table 3 Showing the effect of severity of osteoporosis in 3 groups with different authors**

| Study | Asthma | ACOS | COPD |
|---|---|---|---|
| Katsura and Kida | * | * | *** |
| Torch | -- | -- | -- |
| Jee, et al., | * | *** | *** |
| Present study | ** | *** | ** |
| *Represents the effect of severity in the above-mentioned table | | | |

The secondary objective is also fulfilled as the decreased bone mineral density is suggested with the decreased vitamin D and body mass index that intern decreases the lung capacity. Supported by the significant negative relationship of 25-OHD with the number of exacerbations, GINA class of asthma severity and inhaled corticosteroid dose. Comparison of vitamin D levels with the previous studies is shown in Table 4.

**Table 4 Vitamin D levels of the present study compared with the other relevant study**

| Study | Insufficiency | Deficiency |
|---|---|---|
| Rafiq, et al., | 17.5% | 75.5% |
| Present study | 61.5% | 35.5% |

Among the total cases, 6 cases were normal, 123 were osteopenia and 71 were osteoporosis cases. Finally the effect of decreased bone mineral density, vitamin D decreases the absorption of calcium. As a result of decreased body mass index with various comorbidities may add burden to the lung with the decrease of trace elements.

## CONCLUSION

Our findings clearly show that the effect of disease and inhaled corticosteroids use in respiratory diseases for a longer duration or in high doses resulting in decreased bone mineral density along with the decreased body mass index. Vitamin D deficiency and insufficiency is also playing a role in decreased lung capacity. Even though the participants are belonging to the rural area, people are below the poverty line; because of dietary insufficiency, they may have these respiratory problems with their drug effect.

So, the health care professionals should educate the patients to increase focus on lifestyle, identify and avoid irritants as much as possible and use of limited doses are needed. To balance the drug effect, we need to suggest the importance of intake of a balanced diet, dietary supplements, and regular check-ups with various investigations we can manage the health condition. Lastly depending on the occupational exposure to sunlight and physical activity should be recommended even for healthy individuals also.

## DECLARATIONS

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**Ethical Approval**

The study was approved by the Institutional Ethics Committee, NRI Institute of Medical Sciences, Visakhapatnam.

**Conflict of Interest**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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