

# Growth Hormone, Testosterone and Vitamin-D Levels in Patients of Chronic Obstructive Pulmonary Disease.

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## ABSTRACT

**Background:** Chronic obstructive pulmonary disease (COPD) is no longer considered to affect only the lungs and airways but also the rest of the body. The systemic manifestations of COPD include cardiovascular disorders, musculoskeletal dysfunction, psychiatric disturbances and a number of endocrine disorders, such as those involving the pituitary, the thyroid, the gonads, the adrenals and the pancreas. The mechanisms by which COPD alters endocrine function are incompletely understood but likely involve hypoxaemia, hypercapnia, systemic inflammation and glucocorticoid administration. Altered endocrine function can worsen the clinical manifestations of COPD through several mechanisms, including decreased protein anabolism, increased protein catabolism, non-enzymatic glycosylation and activation of the renin angiotensin-aldosterone system. Systemic effects of endocrine disorders include abnormalities in control of breathing, decreases in respiratory and limb-muscle mass and function, worsening of respiratory mechanics, impairment of cardiac function and disorders of fluid balance. Though endocrine disorders in COPD involve pituitary, thyroid, gonads, adrenals and pancreas, we have observed just the two hormone levels i.e:- testosterone and growth hormone as there are very fewer studies conducted on these parameters in the past.along with it vitamin-D levels are also noted as musculoskeletal dysfunction is common in patients of COPD. **Objectives:** To know whether there is any imbalance noted in the levels of growth hormone, testosterone and vitamin-D in the patients of COPD. **Methods:** Retrospective observational analysis was done on the patients of COPD who were admitted at our hospital. A total of 200 patients who were diagnosed as COPD was taken into the study sample. After the thorough clinical history and examination, patients underwent with routine blood investigations, chest radiograph and pulmonary function tests. After the establishment of diagnosis of COPD, a written informed consent was taken from the patients who were willing to be part of this study. Just 80 patients accepted to participate in the study and the samples of those patients were sent for growth hormone, testosterone and vitamin-D analysis. **Results:** The sample size of study consists of 80 patients, who were diagnosed as COPD. Out of 80 patients of COPD, 12 patients(15%) had deficiency in the levels of growth hormone, while 68 patients(85%) had normal levels. Out of the 80 patients of COPD, 8 patients (10%) had deficiency in the levels of testosterone, while 72 patients (90%) had levels within range. Out of 80 patients of COPD, 16 patients (20%) had vitamin-D deficiency, 4 patients (5%) had indeterminate values and 60 patients (75%) had normal values. **Conclusion:** By observing the results of this study, we can say that there may be disturbances found in the levels of growth hormone, testosterone and vitamin-D in the patients of COPD. So, endocrinological derangements can be found in the patients of COPD.

**Keywords:** COPD, GROWTH HORMONE, TESTOSTERONE, FEV1, 25-oh vit-D.

## INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD), the third leading cause of death in the world, causes 3.1 million deaths worldwide and represents an important public health challenge that is both preventable and treatable.<sup>[1]</sup> Total deaths from COPD are projected to increase by more than 30% in the next 10 years without interventions to cut risks, particularly exposure to tobacco smoke.<sup>[1]</sup> COPD is a major cause of chronic morbidity and mortality throughout the world; many people suffer from this disease for years, and die prematurely from it or its complications. Globally, the COPD burden is projected to increase in coming decades because of

continued exposure to COPD risk factors and ageing of the population.

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The disease causes a heavy burden on the global health care resources. The costs involved in the treatment and evaluation is directly proportional to the pulmonary and the extra pulmonary components of the disease.

‘Chronic obstructive pulmonary disease (COPD) is as a “preventable and treatable disease with some

significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary components characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.<sup>[2]</sup>

The pathogenesis and clinical manifestations of COPD are not just restricted to pulmonary inflammation and structural remodeling. Rather, this disorder is associated with clinically significant systemic alterations in biochemistry and organ function. The systemic aspects of COPD include oxidative stress and altered circulating levels of inflammatory mediators and acute-phase proteins. As in other chronic inflammatory conditions, weight loss, muscle wasting and hypoproteinemia are commonly seen in COPD patients. Selective wasting of fat-free mass coupled with impaired respiratory and peripheral muscle function and a reduced capacity for exercise occur in COPD patients. Indeed, weight loss may directly impact poor prognosis in COPD patients.<sup>[5]</sup>

#### **Systemic Involvement in COPD**

The pathogenesis and clinical manifestations of COPD are not restricted to pulmonary inflammation and structural remodeling. Rather, this disorder is associated with clinically significant systemic alterations in biochemistry and organ function. As in other chronic inflammatory conditions, weight loss, muscle wasting, and tissue depletion are commonly seen in COPD patients.

Wasting is a generally occurring manifestation in a wide variety of different chronic conditions and can be considered to be an important systemic manifestation as a loss of > 40% of actively metabolizing tissue is incompatible with life. The body cell mass (BCM) represents the actively metabolizing (organs) and contracting (muscles) tissue. This BCM cannot be measured directly. Changes in BCM can be clinically recognized by decrease in body mass index (BMI) in general and by loss in fat-free mass (FFM) in particular. In a retrospective study of 400 patients with COPD, Schols et al demonstrated that low body mass index (BMI), age, and low PaO<sub>2</sub> were significant independent predictors of increased mortality rates. After stratification of the group into BMI quintiles, a threshold value of 21 kg/m<sup>2</sup> was identified below which the mortality risk was clearly increased.

The mechanisms by which COPD alters endocrine function are incompletely understood but likely involve hypoxaemia, hypercapnia, systemic inflammation and glucocorticoid administration.

Altered endocrine function can worsen the clinical manifestations of COPD through several mechanisms, including decreased protein anabolism, increased protein catabolism, non-enzymatic glycosylation and activation of the rennin-angiotensin-aldosterone system. Systemic effects of

endocrine disorders include abnormalities in control of breathing, decreases in respiratory and limb-muscle mass and function, worsening of respiratory mechanics, impairment of cardiac function and disorders of fluid balance. Research on endocrine manifestations of COPD embraces techniques of molecular biology, integrative physiology and controlled clinical trials. A sound understanding of the various disorders of endocrine function associated with COPD is prudent for every physician who practices pulmonary medicine. In our study we analyzed the variation in growth hormone, testosterone and vitamin-D levels.

#### **COPD and Growth Hormone**

The human growth hormone (hGH) is a polypeptide composed of 191 amino acids released by the hypophysis resulting from certain specific physiological stimuli. Through techniques of genetic engineering, it is possible to obtain its synthetic form, recombinant hGH (rhGH). This substance can accelerate the oxidation of fatty acids and increase the capture of amino acids, in addition to exerting a diabetogenic effect secondary to the decreased transfer of glucose through the cellular membrane. Other rhGH-related side effects include peripheral edema, hypothyroidism and gynecomastia.

The hGH stimulates the liver to produce insulin-like growth factor 1, a molecule that binds to plasma proteins. This growth factor is the most important anabolic mediator of hGH and plays a central role in regulating metabolism, as well as in cell proliferation and differentiation. Therefore, the use of hGH has potentially benefits in COPD. Some authors have evaluated the effect of rhGH in patients with advanced COPD (FEV<sub>1</sub> = 29 ± 6% of predicted) via subcutaneous administration (30 mg/kg/day for four days, and later on 60 mg/kg/day for four more days), in 6 patients with weight loss who were receiving parenteral nutrition. The administration of the rhGH was accompanied by increased baseline energy expenditure and oxidation of fats, in addition to decreased glucose oxidation. An improvement in nitrogen balance, which is a potentially relevant effect for patients with low body weight, was observed. Other authors 76 analyzed the effects of rhGH supplementation (0.05 mg/kg/day of subcutaneous administration for 3 weeks) in 7 patients with COPD (FEV<sub>1</sub> < 70% of predicted) and low body weight (< 90% of ideal weight). There was significant weight gain and improved nitrogen balance. In functional terms, respiratory muscle strength, evaluated by maximal inspiratory pressure, increased by an average of 33% in 6 patients and decreased by 8% in 1. There were no changes in respiratory muscle endurance. In another study, the effects of rhGH administration (0.15 IU/kg/day of subcutaneous administration for 3 weeks) was evaluated in 16 stable patients (FEV<sub>1</sub> < 70% of predicted and body weight < 90% of ideal). The

authors observed an increase in muscle mass, although without any accompanying increase in respiratory muscle performance or exercise capacity. Secondly, there was increase in the baseline energy expenditure and an elevation of the metabolic rate (oxygen consumption and production of carbon dioxide) attributed to the thermogenic effect of rhGH, in addition to the increase in protein renovation and lipolysis. The effects of rhGH on the functional capacity of patients with COPD are controversial and should be carefully analyzed due to the reduced number of publications, lack of control groups and isolated (without physical training) use of ergogenic therapy. In addition, the studies were carried out for a short period of time (approximately 3 weeks), showing acute alterations in metabolism and muscle strength. Therefore, the long-term effects of rhGH administration remain unknown. Another aspect to be explored in future studies is the cost-effectiveness ratio, since rhGH supplementation is expensive and, as previously stated, its clinical benefits have yet to be demonstrated. These aspects, together with the limitation of subcutaneous administration, can explain why no studies of rhGH use in COPD have been published in the last eight years.

#### **COPD and testosterone levels**

Middle-aged and elderly men exhibit a decline in the concentration of serum testosterone. When excessive, this decline may contribute to diminished energy level, libido, bone density, and muscle mass. This constellation of signs and symptoms has been termed late-onset hypogonadism, symptomatic late-onset hypogonadism, androgen deficiency in the aging male, or andropause. The observation that many patients with COPD, most of whom are middle-aged or elderly, fit the profile of late-onset hypogonadism has spurred a flurry of research on the incidence, functional impact, and possible treatment of this abnormality.

Van Vliet and coworkers [74] extend our knowledge on late-onset hypogonadism in men with COPD. They compared, for the first time, patients with COPD and age-matched control subjects. Half of the 78 patients with COPD had low levels of free testosterone, whereas a quarter of the 21 control subjects were hypogonadal. First, the prevalence of hypogonadism in the small control group of Van Vliet and colleagues is much lower than the 34 to 40% prevalence of hypogonadism for subjects in their 60s and then the near 70% prevalence for subjects in their 70s reported in population studies in North America and Europe. Second, when the data of Van Vliet and colleagues are pooled with three other recent studies, the overall prevalence of hypogonadism in men with COPD is 43%. This is within the range reported in population studies of generally healthy men of the same ages. Third, the conclusion that late-onset hypogonadism in men

with COPD is not something unique to these patients and probably not different from late-onset hypogonadism in the general population is further supported by the lack of correlation between testosterone levels and severity of obstruction or with potential causes of hypogonadism specific to patients with COPD, such as hypoxemia or glucocorticoid therapy. The similar prevalence of comorbidities in the hypogonadal and eugonadal men with COPD, reported for the first time by Van Vliet and colleagues, further supports the possibility that hypogonadism in these patients is not a different entity from late-onset hypogonadism in the general population.

In their investigation, Van Vliet and coworkers noted a correlation between quadriceps strength and testosterone concentrations. This finding adds information to a complex and often contradictory body of literature. For instance, Debigare and associates reported that the prevalence of hypogonadism among men with COPD is equivalent among patients with and without muscle wasting. Similarly, we recorded no difference in quadriceps strength (and endurance) between hypogonadal and eugonadal men with COPD. In addition, when Bhasin and colleagues administered a long-acting gonadotropin-releasing hormone agonist to induce hypogonadism in elderly men and then supplemented the men with subtherapeutic doses of testosterone enanthate, they found no difference in fat free mass or muscle strength. When the same investigators doubled the circulatory levels of total and free testosterone by administering higher doses of testosterone enanthate, the increases in fat free mass and strength were within the noise of the measurement. The same team of investigators, however, reported a 17% increase in quadriceps strength (and endurance) when administering 100 mg/week of testosterone enanthate for 10 weeks to men with COPD undergoing resistance training. It is not known why low testosterone should cause decreased strength in some series and not in others, nor whether the statistical differences in quadriceps strength—when present—are clinically important.

Despite less quadriceps strength among their hypogonadal patients, Van Vliet and colleagues reported equivalent exercise capacity (6-minute walk distance) in the two groups of patients. This result confirms previous observations of equivalent exercise capacity, quantified either as 6-minute walking distance or maximal bicycle ergometry, in men with COPD with and without hypogonadism. The similar exercise performance in the two groups is also consistent with the observation that administration of anabolic steroids to unselected patients with COPD or testosterone enanthate to men with COPD and variable testosterone levels produces no improvement in whole body exercise capacity.

A crucial question is whether the results of Van Vliet and coworkers support the use of testosterone supplementation in men with COPD who have low testosterone levels. The investigators express caution. Men who have COPD and low testosterone levels do not differ from their eugonadal counterparts in respiratory symptoms, quality of life, respiratory muscle strength and endurance, and exercise capacity. Therefore, it is difficult to justify that goals of replacement therapy are to improve these parameters. Replacement therapy does not increase exercise capacity or respiratory muscle strength in these patients. The use of testosterone replacement therapy to increase quadriceps strength in patients participating in rehabilitation programs is promising, but requires larger trials.

The caution expressed by Van Vliet and colleagues on whether (or not) to advocate testosterone replacement in men with COPD and low testosterone levels reflects the ongoing controversy regarding indications for testosterone replacement in older men in general. Long-term testosterone supplementation can be associated with side effects, including increase in hematocrit, sleep apnea, and prostatic hypertrophy. The effects of testosterone administration on the risk of atherosclerotic heart disease and prostate cancer remain unknown because all current studies are underpowered to answer these questions. For example, more than 6,000 elderly hypogonadal men randomly assigned to receive testosterone or placebo for 6 years would be necessary to determine whether testosterone treatment increases the risk of prostate cancer by 30%. In a recently published report from the Institute of Medicine, an expert committee concluded that unless more convincing studies are published, there is currently insufficient evidence to support testosterone therapy in older men.

### **COPD and Vitamin-D levels**

Vitamin D is essential for bone and muscle health while regulating calcium, phosphate, and bone homeostasis. It was shown to play an important role in the growth of skeletal muscles, muscle contractility, and myogenesis as well as in the development of the growth plate, mineralized bone, and osteoclastogenesis.

In humans, vitamin D deficiency, defined as serum levels below 20 ng/mL (50 nmol/L) was found to be associated with poor muscle strength and performance and decreased physical activity. Due to an imbalance in calcium and phosphate homeostasis, vitamin D deficiency is also known to be a risk factor for severe osteoporotic fractures. In addition, an association between a polymorphism of the vitamin D receptor and bone mineral density has been highlighted [73](#).

The prevalence of vitamin D deficiency in patients with severe and very severe COPD is, respectively, 60% and 77%. Vitamin D deficiency was found to

be correlated with disease severity but not with acute exacerbations and mortality. Several reasons could account for vitamin D deficiency in patients with COPD, including a poor diet, reduced capacity of the aging skin to synthesize vitamin D, absence of outdoor activity and sun exposure, increased catabolism by glucocorticosteroids, impaired activation due to renal dysfunction, and lower storage capacity in muscles or fat, due to wasting.

In patients with COPD, a relationship was found between variants in the vitamin D receptor gene and skeletal muscle strength but, although an association was observed between vitamin D levels and muscle strength in control patients, this association was not present in patients with COPD. This observation might indicate that some patients with COPD may be resistant to the actions of vitamin D, which was corroborated by elevated levels of PTH in these patients. Plasma concentration of vitamin D was found to be positively correlated with bone mineral density and functional exercise capacity in patients with COPD, and with an increased risk of osteoporosis in these patients.

## **MATERIALS AND METHODS**

Retrospective observational analysis was done on the patients of COPD who were admitted at our hospital. A total of 200 patients who were diagnosed as COPD was taken into the study sample. After the thorough clinical history and examination, patients underwent with routine blood investigations, chest radiograph and pulmonary function tests. After the establishment of diagnosis of COPD, a written informed consent was taken from the patients who were willing to be part of this study. Just 80 patients accepted to participate in the study as many of the others had affordability issues and the samples of those patients were sent for growth hormone, testosterone and vitamin-D analysis.

### **Inclusion criteria**

As per GOLD guidelines,<sup>[2]</sup>

Any patient who has symptoms of chronic cough, sputum production or dyspnea.

The values of Forced Expiratory Volume in first second (FEV1) less than 80% of the expected value and ratio of forced expiratory volume in first second to the forced vital capacity less (FEV1%) than 0.7 (70%) after post bronchodilator inhalation were included in this study.

### **Exclusion criteria**

- Recent myocardial infarction < 4months.
- Unstable angina.
- Congestive heart failure (NYHA class III or IV).
- Inability to perform spirometry or 6 minute walk test.
- Unrelated life threatening major illness.

- Liver disease.
- Patients with acute exacerbation.
- Female sex.

### Statistical analysis

The Statistical software namely SPSS 20.0 was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables.

## RESULTS & DISCUSSION

The sample size of study consists of 200 patients, who were diagnosed as COPD. Out of which 80 patients accepted to participate in the further study. Out of 80 patients of COPD, 12 patients (15%) had deficiency in the levels of growth hormone, while 68 patients (85%) had normal levels. Out of the 80 patients of COPD, 8 patients (10%) had deficiency in the levels of testosterone, while 72 patients (90%) had levels within range. Out of 80 patients of COPD, 16 patients (20%) had vitamin-D deficiency, 4 patients (5%) had indeterminate values and 60 patients (75%) had normal values.

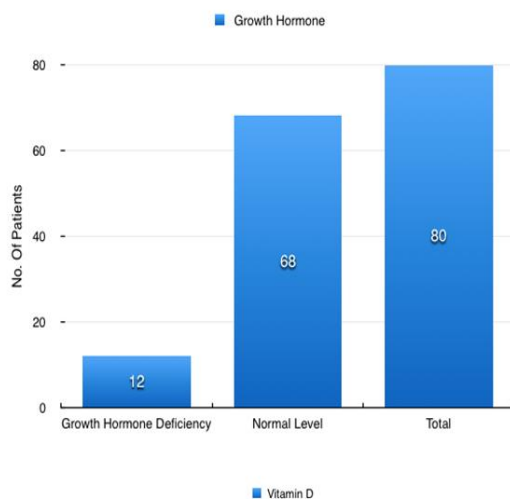


Figure 3: Growth Hormone levels.

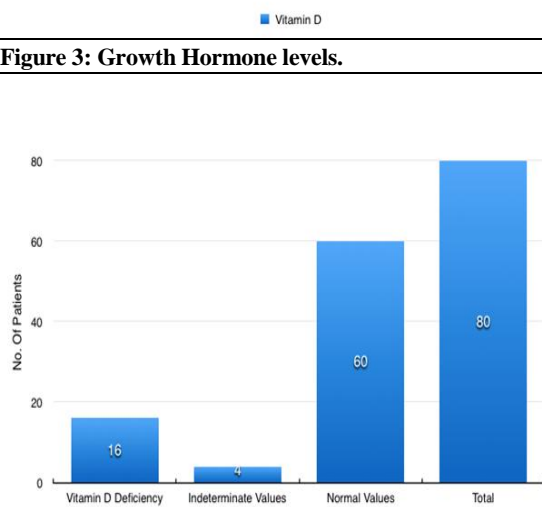


Figure 3: Vitamin D levels.

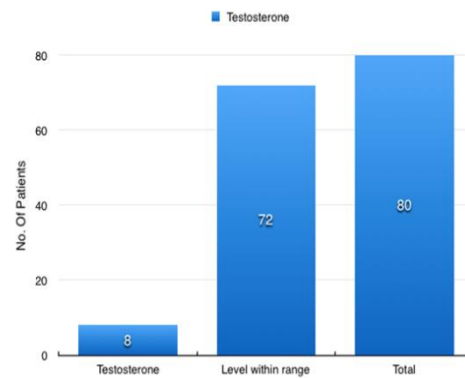


Figure 3: Testosterone levels.

## CONCLUSION

By observing the results of this study, we can say that there may be disturbances found in the levels of growth hormone, testosterone and vitamin-D in the patients of COPD. As follow up was not done, an extension of this study is necessary to establish the role of hormonal therapy in the patients of COPD. So, we conclude that endocrinological derangements can be found in the patients of COPD.

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