Relationship between Serum Levels of Testosterone and the Severity of Chronic Obstructive Pulmonary Disease

Seyed Ali-Javad Mousavi 1, Mohammad-Reza Kouchari 2, Seyed Hossein Samdani-Fard 3, Zahra Nasihati Gilvae 3, Mohsen Arabi 3

Background: This cross-sectional study aimed to investigate the relationship between the levels of serum testosterone and the severity of chronic obstructive pulmonary disease (COPD).

Materials and Methods: Using GOLD criteria, 140 male patients with COPD were categorized into mild, moderate, severe and very severe COPD groups of 35 each. Then, serum levels of testosterone, prolactin and LH of patients were compared and the data were analyzed using SPSS version 18 software.

Results: Average age of patients was 67.4±10.1 years (range 41 to 90 years). The prevalence of the secondary hypogonadism was 58.6%. It was shown that the level of serum testosterone was directly correlated with the severity of COPD (P= 0.04).

Conclusion: This study found that the prevalence of the secondary hypogonadism in COPD patients was high. The forced expiratory volume in 1 second (FEV1) was correlated with the level of serum testosterone. Further investigations are required to better evaluate the pathology and treatment of secondary hypogonadism in COPD patients.

Key words: Chronic Obstructive Pulmonary Disease, Testosterone, Serum level

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a group of respiratory diseases characterized by airflow limitation that is not fully reversible, and is associated with cough, sputum production and dyspnea and is defined by reduced forced expiratory volume in 1 second (FEV1) and FEV1/FVC ratio on lung function tests. In advanced conditions, COPD is associated with involuntary weight loss and muscle wasting. The association between low body mass index (BMI) and poor prognosis in patients with COPD is a common clinical observation and reduced BMI is considered as an independent predictor of COPD (1).

It has been shown that men suffering from advanced COPD have lower levels of endogenous testosterone and the changes in the levels of the sex hormone are associated with hypoxia, hypercapnia, and reduced FEV1(2-10).

In this study, the FEV1/FVC ratio in patients suffering from COPD was determined and the correlation between the levels of serum testosterone and the severity of COPD was evaluated. The results can provide a better insight for treatment of hypogonadism following COPD.
MATERIALS AND METHODS

In this cross-sectional study, 140 patients suffering from COPD were investigated.

Using a spirometry test, the patients with COPD who did not respond to bronchodilator were considered eligible to enter the study.

Those who had a history of primary or secondary hypogonadism, pituitary adenomas, or the patients with a benign prostatic hypertrophy requiring surgical intervention or administration of 5-alpha-reductase inhibitors, and alcohol consumers or patients with chronic kidney disease were excluded.

To calculate the BMI, the subjects' weight and height were measured. The average levels of total serum testosterone, luteinizing hormone (LH) and prolactin were determined. Pulmonary function was determined using a JAEGER spirometer (CareFusion Corp., CA, USA) and salbutamol inhaler as a bronchodilator. Total serum level of testosterone was measured with an electrochemiluminescence immunoassay (Hitachi ECL, Japan) and using Roche kit (Germany) (with a normal range of 2.8-8.8 ng/ml). The serum levels of LH and prolactin were determined using a gamma counter and Immunotech radioimmunoassay (RIA) kit (Beckman Coulter, France) (with a normal range of 0.5-18 mLU/mL and 1-18 ng/mL, respectively).

By using spirometry and according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, the severity of the COPD in patients was classified into mild, moderate, severe and very severe groups. All patients in each group were compared for age, BMI, blood levels of testosterone, LH and prolactin. Subjects who had a FEV1/FVC <0.70 were classified into four COPD severity groups (35 patients each) based on GOLD criteria: FEV1 ≥80% of predicted (mild stage), 50% ≤FEV1 <80% of predicted (moderate stage), 30% ≤FEV1 <50% of predicted (severe stage), FEV1 < 30% of predicted (very severe stage). All patients in each group were compared for age, BMI, blood levels of testosterone, LH and prolactin. There was no significant difference in the average age (P =0.58) and number of smokers (P =0.07) between groups (Table 1).

In our study, from 140 patients with COPD, 82 cases (58.6%) had a testosterone level of less than 2.8 ng/mL, indicating a hypogonadism in these patients.

The results showed that serum levels of testosterone in patients with severe stage of COPD were the lowest and in the group with mild stage of COPD, it was the highest; this difference was statistically significant (P=0.04).

There was a significant correlation between BMI and FEV1 in all groups (P=0.02).

The serum level of LH in all patients was lower or within the normal range and its average was significantly different between the groups (P<0.001).

RESULTS

In this study, 140 male patients with COPD were investigated. The average age was 61.3 ± 4.67 years (range 41 to 90 years). Demographic characteristics like BMI and number of smokers are listed in Table 1.

From 140 patients, 101 (72.1%) had a smoking history, with an average consumption of 28.5±9.9 packs per year and no significant differences were found for the percentage of smokers between the groups (P=0.07).

Table 1. Demographical parameters and the level of serum hormones in COPD patients

| Parameter       | Mild (n=35) | Moderate (n=35) | Severe (n=35) | Very severe (n=35) | P Value |
|-----------------|------------|----------------|--------------|-------------------|---------|
| Age (years)     | 67.3±7.5   | 69.4±11.6      | 66.9±11.5    | 66.2±9.2          | 0.58    |
| BMI (kg/m²)     | 25.6±3.01  | 25.5±4.5       | 24.9±3.4     | 23.1±3.4          | 0.02*   |
| Smoking (%)     | 71.4       | 62.9           | 65.7         | 88.6              | 0.07    |
| Testosterone level (ng/mL) | 3.4±1.09   | 2.4±1.7        | 2.36±1.6     | 2.30±0.96         | 0.04*   |
| LH level (mIU/mL) | 11.2±2.1   | 10.2±2.5       | 7.2±3.3      | 6.6±2.1           | 0.001*  |
| Prolactin (ng/mL) | 9.2±3.1    | 10.02±3.9      | 10.2±3.2     | 11.2±4            | 0.13    |

*P values with significant differences.
Twenty-eight out of 140 patients (20%) in this study had an addiction to opium, of those, 19 patients had hypogonadism and 9 patients were eugonadal. Using the Post-Hoc analysis, the paired-comparison of groups showed a significant difference between the mild and very severe groups (\( P<0.001 \)), mild and severe groups (\( P=0.02 \)) and between the mild and moderate groups (\( P=0.005 \)).

The serum levels of prolactin in the very severe group were higher than in the mild group, but it was not statistically significant (\( P=0.13 \)).

**DISCUSSION**

In the current study, 140 patients with COPD were investigated using spirometry and were categorized into 4 groups based on GOLD criteria.

The average age of patients was not significantly different between the groups. Thus, since the patients in all groups were matched for age and smoking habit, the findings regarding blood levels of testosterone appear not to be biased by these factors.

It was shown that the BMI in the patients with very severe stage of COPD was lower than in others, indicating a progressive and chronic state of losing weight and muscle wasting in these patients.

The percentage of COPD patients with hypogonadism was 58.6%. Different prevalence for hypogonadism in patients with COPD reported in previous studies (7,11) may be due to the differences in sex, age and race.

In an investigation by Mulligan et al., 36.2% of 2,152 over 45 year-old male patients with COPD had hypogonadism (12). In a review by Balasubramanian, the prevalence of hypogonadism in COPD patients was indicated to be 22-69% (13).

In the current study, it has been shown that in patients suffering from very severe COPD with the lowest FEV1, the testosterone level was less than in other groups, while it was greater than the group with mild COPD and the highest FEV1 (\( P<0.001 \)). Similar correlation between the FEV1 and the serum levels of testosterone has been shown previously (4).

COPD is associated with secondary hypogonadism, which is characterized by normal or low range of serum LH levels (14). Similar pattern was shown by the current study.

Chronic illnesses, COPD, steroids, opium and hyperprolactinemia can suppress the gonadotropin secretion by central nervous system (15). As shown in our study, the percentage of hypogonadism in opium addicts was higher than in those with eugonadism (23.2% vs. 15.5%).

Except for the very severe COPD group, the serum level of prolactin was within normal range. The greater amount of prolactin level in patients with very severe COPD could be caused by regulatory effect of nicotine on the secretion of prolactin (16). The increased prolactin can reduces the secretion of LH and testosterone by affecting the hypothalamic-pituitary pathway.

In conclusion, the current study showed that COPD patients had a high prevalence of secondary hypogonadism (58.6%). As the hypogonadism is associated with increased rates of depression in patients with osteoporosis and impairs life quality, performing further prospective and interventional investigations on COPD patients with hypogonadism might provide better insights for understanding its pathology and treatment.

**REFERENCES**

1. Reilly JJ, Silverman EK, Shapiro SD. Chronic Obstructive Pulmonary disease. In: Londo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J (eds): Harrison's principles of internal medicine18th ed. New York:McGraw-Hill; 2012.p.2151-4
2. Karadag F, Ozcan H, Karul AB, Yilmaz M, Cildag O. Sex hormone alterations and systemic inflammation in chronic obstructive pulmonary disease. *Int J Clin Pract* 2009; 63 (2): 275-81.
3. Akbaş T, Karakurt S, Unlügüzel G, Celikel T, Akalin S. The endocrinologic changes in critically ill chronic obstructive pulmonary disease patients. *COPD* 2010; 7 (4): 240-7.
4. Svartberg J, Schirmer H, Medbø A, Melbye H, Aasebø U. Reduced pulmonary function is associated with lower levels
of endogenous total and free testosterone. The Tromsø study. Eur J Epidemiol 2007; 22 (2): 107-12.

5. Van Vliet M, Spruit MA, Verleden G, Kasran A, Van Herck E, Pitta F, et al. Hypogonadism, quadriceps weakness, and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005; 172 (9): 1105-11.

6. Kamischke A, Kemper DE, Castel MA, Lüthke M, Rolf C, Behre HM, et al. Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. Eur Respir J 1998; 11 (1): 41-5.

7. Laghi F, Antonescu-Turcu A, Collins E, Segal J, Tobin DE, Jubran A, et al. Hypogonadism in men with chronic obstructive pulmonary disease: prevalence and quality of life. Am J Respir Crit Care Med 2005; 171 (7): 728-33.

8. Svartberg J. Androgens and chronic obstructive pulmonary disease. Curr Opin Endocrinol Diabetes Obes 2010; 17 (3): 257-61.

9. Snyder PJ. Hypogonadism in elderly men—what to do until the evidence comes. N Engl J Med 2004; 350 (5): 440-2.

10. Biskobing DM. COPD and osteoporosis. Chest 2002; 121 (2): 609-20.

11. Laghi F, Langbein WE, Antonescu-Turcu A, Jubran A, Bammert C, Tobin MJ. Respiratory and skeletal muscles in hypogonadal men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005; 171 (6): 598-605.

12. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract 2006; 60 (7): 762-9.

13. Balasubramanian V, Naing S. Hypogonadism in chronic obstructive pulmonary disease: incidence and effects. Curr Opin Pulm Med 2012; 18 (2): 112-7.

14. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006; 91 (6): 1995-2010.

15. Bhasin S, J Larry Jameson JJ. Disorders of the testes and male reproductive. In: Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J (eds): Harrison's principles of internal medicine 18th ed. New York: McGraw-Hill; 2012.p.3017-8.

16. Benowitz NL, Brunetta PG. Smoking hazards and cessation. In: Mason RJ, Broaddus VC, Martin T, King T, Schraufnagel D, Murray JF, Nadel JA (eds): Murray and Nadel's Textbook of Respiratory Medicine, 5th ed. Philadelphia, PA: Saunders/Elsevier; 2010.p.1320-22.