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Hypogonadism in patients with chronic obstructive pulmonary disease: relationship with airflow limitation, muscle weakness and systemic inflammation

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Abstract *Objectives:* To determine the prevalence of hypogonadism in male patients with Chronic obstructive pulmonary diseases (COPD), and to study its impact on skeletal muscle dysfunction and assess the effect of systemic markers of inflammation on testosterone level and muscle function. The study included 50 stable male COPD patients and 30 controls.
Methods: Both groups were subjected to the following measurements; inflammatory markers levels (high-sensitivity C-reactive protein (hs-CRP) and interleukin – 6 (IL-6)), sex hormones including; serum total (T) and free testosterone (FT), sex hormone binding globulins (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and 17β estradiol levels (E2), the exercise capacity (6-minute walk distance (6MWT)) and quadriceps muscle force (One repetition maximum (1RM) and EMG). COPD patients underwent spirometry.
Results: There was a higher prevalence of hypogonadism in COPD patients than the controls (62% versus 17%). There was a significant negative correlation between serum testosterone levels (T and

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FT) and the severity of airway obstruction. Quadriceps muscle force and the exercise capacity were significantly lower in COPD patients than controls but they showed no correlation with the testosterone level. Inflammatory markers were significantly higher in COPD patients compared to controls and showed a significant correlation with the severity of airflow obstruction. The higher inflammatory markers levels were related to more muscle weakness as hs-CRP was inversely correlated with the quadriceps strength and exercise capacity, while IL-6 was inversely correlated to quadriceps strength only.

Conclusion: Hypogonadism is highly prevalent in clinically stable COPD patients and is particularly related to the severity of the airway obstruction. Systemic inflammation is present in stable COPD patients and its intensity is related to the severity of the underlying disease and it predisposes to skeletal muscle weakness and exercise intolerance. However, we failed to find a significant association between hypogonadism and muscle weakness or systemic inflammation.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a systemic disease characterized by multiple extra pulmonary manifestations, including cachexia and skeletal muscle dysfunction which can contribute to morbidity and mortality.[1]

Peripheral muscle dysfunction, a common systemic complication in patients with COPD, commonly results from muscle wasting. This dysfunction is associated with decreased exercise capacity, muscle weakness, impaired quality of life, and decreased survival.[2,3]

The presence of a low-grade systemic inflammation can be implicated in the pathogenesis of these extra pulmonary manifestations including skeletal muscle dysfunction and hypogonadism.[4]

It was observed that many patients with COPD, most of whom are middle-aged or elderly, fit the profile of late-onset hypogonadism[5–7] manifested by diminished energy level, libido, bone density, and muscle mass.[8,9]

Patients are defined as being hypogonadal when they have androgen deficiency combined with otherwise unexplained fatigue or diminished energy, a diminished sense of vitality, or a diminished sense of well-being (all commonly experienced by patients with COPD).[7–10]

Prevalence of hypogonadism in men with COPD can range from 22% to 69% and has been associated with several other systemic manifestations including osteoporosis, depression, and muscle weakness.[11]

Several observations suggest that hypogonadism may contribute to the muscle dysfunction seen in men with COPD. First, hypogonadism has a high prevalence among these patients. Second, hypogonadism can cause decreases in nitrogen retention, lean body mass, and body weight. Third, proinflammatory cytokines, which are increased in some patients with COPD with muscle wasting, can, lead to decreased testosterone production. Fourth, testosterone deficiency can contribute to elevated levels of interleukin-6, an inflammatory, procatabolic cytokine. Finally, administration of testosterone can increase myofibrillar protein synthesis and decrease protein breakdown.[2]

It has been observed that muscle weakness is not completely reversed even after long periods months of exercise training.[12] Therefore, factors other than physical inactivity may predispose to the development of muscle weakness in patients with COPD.[13,14]

Because of the clinical impression that systemic inflammation as well as hypogonadism plays a significant role in the pathogenesis of skeletal muscle dysfunction in patients with COPD, a case-control study was designed to determine the prevalence of hypogonadism in a sample of male patients with COPD, to study the impact of hypogonadism on skeletal muscle dysfunction and to assess the effect of systemic markers of inflammation on testosterone level and muscle function.

2. Subjects and methods

The present study is a case control study that was done in, Faculty of Medicine, Alexandria University, as a collaborate work between pulmonary, internal medicine and physical medicine departments, and medical research institute; department of chemical pathology. The study protocol was approved by the local ethics committee. Written informed consent according to the hospital policy guidelines was obtained from all patients and controls before initiating any study – related activity.

2.1. Subjects

The study population consisted of 50 male patients with stable COPD with no history of recent exacerbation and 30; age-matched, healthy control subjects. The diagnosis of COPD was based on smoking history and on pulmonary function test results showing irreversible airflow limitation.[15] All patients were subjected to thorough history taking, including treatment profile and complete physical examination.

2.1.1. Exclusion criteria

Included comorbidities which may interfere with the results of the sex hormones profile (e.g. prostate carcinoma, liver cirrhosis) and current androgen and anti-androgen therapy. Any chronic diseases, such as chronic heart failure or diabetes, active inflammatory diseases or primary diagnosis of obstructive sleep apnea syndrome. Subjects who received systemic steroids within the 4 months prior to the study. Patients with Hemoglobin level less than 13 g were excluded from the study to rule out the effect of anmia on sex hormone level or muscle function.

2.2. Laboratory Investigations:

Samples were collected in fasting state in the morning. Sample collection, processing, and storage were done according to the kits instructions. The following measurements were done:

2.2.1. Markers of systemic inflammation:

Including high sensitivity CRP (hs-CRP) using a high sensitivity latex assay (lower limit of detection $\leqslant 0.79$ mg/dl) on the Olympus autoanalyzer and IL-6 by Enzyme-Linked Immunosorbant assay (ELISA) using a commercially available kit Immunodiagnostic AG, Stubenwold-Alke 8a D64625 Benshemin according to manufacturer's instructions.

2.2.2. Sex hormones:

Serum concentrations of free testosterone (FT), total testosterone (T), sex hormone binding globulins (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and 17β estradiol levels (E_2) using chemiluminescence technique (IMMULITE 2000 analyzer).

2.3. Six-minute walking distance:

A six-minute walking test was performed according to standard procedure and was used as a measure of exercise capacity. Patients were asked to walk on a 20 m course over a 6 min period. Then the distances covered by the patients during this time interval minutes were recorded.[16]

2.4. Pulmonary function tests:

All patients underwent standard spirometry before and after bronchodilator inhalation according to American Thoracic Society/European Respiratory Society standards.[17]

2.5. Quadriceps muscle force:

One repetition maximum (1RM) was assessed for the quadriceps muscle. This was done using knee extension machine with pelvic strap. Subjects were asked to do few repetitions of knee extension to warm-up. After that, a resistance that is thought to be slightly less than 1RM value was chosen and the subject performed knee extension for one repetition. Subjects were left to rest for one minute then another trial was done against a higher resistance until the true 1RM value was achieved.[18]

2.6. Electromyography (EMG):

Needle EMG was done for the quadriceps muscle (rectus femoris). Rest potentials and motor unit action potentials (MUAP) were assessed.

2.7. Statistical analysis

Data were collected, tabulated, then analyzed using SPSS Ver.13. Qualitative data were presented as numbers and percentage. Quantitative data were expressed as means and standard deviation. Differences between the groups were analyzed by using the student's unpaired *t*-test and $\chi 2$ tests where appropriate. Correlations between different parameters were evaluated using Pearson's rank correlation analysis. A 5% level was chosen as a level of significance in all statistical tests used in the study.

3. Results

3.1. Patient's characteristics and routine labs

Patients with COPD had mean ± SD age of (55.75 ± 4.03) while it was (53.24 ± 3.3) in the control group. Twenty-nine patients (58%) were current smokers, 19 (38%) were ex-smokers and 2 (4%) were never smoker. Body Mass index (BMI) was (24.87 ± 7.3) in COPD group compared to (21.57 ± 2.6) in the control group. Patients with COPD had Hemoglobin level (Hb) of (14.0 ± 0.7) while it was (15.0 ± 0.3) in the control group. There was no significant difference regarding age, smoking status, BMI or hemoglobin level in both groups. Two patients had mild COPD, 10 moderate. 32 severe and 6 patients suffered very severe COPD[15] (Table 1).

3.2. Hormonal profile

COPD patients had significantly lower levels of total testosterone, free testosterone in COPD patients compared to control group with a p value of 0.004 and 0.015, respectively. On the other hand the SHBG was significantly higher in COPD patients ($P = 0.003$). However, there was no significant difference between mean serum (E_2) level in COPD patients (40.8 ± 6.5) pg/ml and control group (33.7 ± 10.4) pg/ml ($p = 0.057$), While Estrogen/Testosterone ratio (E_2/T ratio) was significantly higher in COPD group (9.5 ± 2.4) compared to control group (5 ± 1.5) ($p < 0.001$). Out of the 50 patients with COPD, 30 patients (60%) were hypogonadal (free testosterone < 50 pg/ml) (16) Table 1. Out of them 22 patients (74%) showed low levels of FSH and LH suggesting hypo gonadotrophic hypogonadism. the remaining 8 (27%) patients showed picture of testicular dysfunction (low serum level of testosterone with high serum levels of FSH and LH). The prevalence of hypogonadism in COPD patients was sig-

Table 1 Characteristics and pulmonary function tests of the studied groups.

	COPD	Controls	*P* value
Age	55.75 ± 4.03	53.24 ± 3.3	NS
Smoking status, n (%)			
Current smoker	29(58)	15(50)	
Ex-smoker	19(38)	11(37)	
Never smoker	2(4)	4(13)	NS
BMI (kg/m^2)	24.87 ± 7.3	21.57 ± 2.6	NS
Hb level (g%)	(14.0 ± 0.7)	15.0 ± 0.3)	NS
COPD level of severity, n (%)			
Mild	2(4)		
Moderate	10(20)		
Severe	32(64)		
Very severe	6(12)	–	–
FEV1 (L)	1.2 ± 0.5	–	–
FEV1 (%)	36.4 ± 13.24	–	–
FEV1/FVC	56 ± 20.6	–	–

Table 2 Hormonal profile of the studied groups.

	COPD	Controls	*P* value
Total testosterone, ng/ml	4.5 ± 1.3	7.1 ± 2.3	0.004*
Free testosterone, pg/ml	48.2 ± 10.2	59.6 ± 11.4	0.015*
Hypogonadism, *n* (%)	30 (60)	5 (17)	0.03*
SHBG, nmol/l	74.9 ± 9.3	57.4 ± 34.6	0.003*
E_2 pg/ml	40.8 ± 6.5	33.7 ± 10.4	0.057
E_2/T	9.5 ± 2.4	5 ± 1.5	<0.001*

* Statistically significant at $p < 0.05$.

nificantly higher than in the control group; 60% versus 17% with a p value of 0.03. In COPD patients, 22 (73%) had concentration for FSH significantly lower than control group (2.3 ± 0.9) mIU/mL versus (4.6 ± 1.2) mIU/mL which signifies hypogonadotropin hypogonadism, while 8 patients (26%) showed significantly higher FSH levels of (7.9 ± 3.2) mIU/mL compared to the control group. LH levels in 74% of COPD patients were significantly lower (2.4 ± 0.9) mIU/mL compared to the control group (3.3 ± 1.2) mIU/mL. Eight (8) patients (22%) showed significantly higher LH levels (6.9 ± 2.1) compared to control group (Table 2).

3.3. Inflammatory markers

Hs-CRP levels were significantly higher in COPD patients (10.7 ± 3.4) mg/l compared to control group (2.3 ± 1.1) ($p < 0.001$).

IL-6 levels were significantly higher in COPD patients (10.7 ± 1.9) ng/ml compared to control group (2.5 ± 0.85) ($p < 0.001$) (Table 3).

3.4. Quadriceps muscle force and six minute walk test (6MWT)

The mean 1RM in COPD group was (8.3 ± 5.1) kg which was significantly lower than control group (29.5 ± 4.8) kg ($p < 0.001$). Also the 6-min walking distance (6MWT) was significantly lower in COPD group (246.1 ± 148.6) m compared to the control group (571 ± 90) m. ($p = 0.003$) (Table 3).

3.5. Electromyography (EMG)

Out of 50 stable male COPD patients, 13 patients (26%) showed abnormal rest potentials and 25 patients (50%) showed myopathic MUAPs (Table 3).

Table 3 Inflammatory markers, quadriceps muscle force and six minute walk test (6MWT) in the studied groups.

	COPD	Controls	*P* value
Hs-CRP, mg//l	10.7 ± 3.4	2.3 ± 1.1	<0.001*
IL-6, ng/ml	10.7 ± 1.9	2.5 ± 0.85	<0.001*
1RM, kg	8.3 ± 5.1	29.5 ± 4.8	<0.001*
6 MWT, m	246.1 ± 148.6	571 ± 90	0.003*
Abnormal rest potentials *n* (%)	13 (26)	None	–
Myopathic MUAPs *n* (%)	25 (50)	None	–

* Statistically significant at $p < 0.05$.

3.6. Correlation between hormonal profile and Pulmonary function tests

Serum testosterone level showed a significant positive correlation with both FEV1 ($r = 0.558$, $p = 0.031$) and FEV1/FVC ratio ($r = 0.828$, $p = 0.003$). Serum free testosterone level showed a significant positive correlation with FEV1 only ($r = 0.675$, $p = 0.032$). E/T ratio was negatively correlated with FEV1 ($r = 0.586$, $P = 0.022$).

3.7. Correlation between hormonal profile and Quadriceps muscle force

There was no significant correlation between the hormonal profile of COPD patients and quadriceps muscle strength (1RM) or the exercise capacity (6MWT).

3.8. Correlation between inflammatory markers and pulmonary function tests

There was a significant negative correlation between hs-CRP and FEV1/FVC ($r = -0.332$, $p = 0.037$) and between IL6 and FEV1% ($r = -0.596$, $p = 0.002$).

3.9. Correlation of inflammatory markers with quadriceps muscle force and six minute walk test (6MWT)

1RM was significantly inversely correlated with hs-CRP and IL-6 ($r = -0.371$, $p = 0.021$ and $r = -0.412$, $p = 0.008$ respectively).

CRP was significantly inversely correlated with 6MWT ($r = -0.311$, $p = 0.036$).

3.10. Correlation between hormonal profile and inflammatory markers

There was no correlation between serum testosterone, free testosterone, SHBG levels or E_2/T ratio and any of the inflammatory markers. There was no correlation between FSH or LH and systemic markers of inflammation.

There was no significant correlation between the sex hormones and other parameters such as age, smoking status, BMI or hemoglobin level.

4. Disscusion

In the present study, we found significant differences in serum levels of sex hormones between male patients with COPD and age matched healthy males. In addition there was a higher prevalence of hypogonadism in the COPD patients than the control subjects (62% versus 17%). Prevalence estimates of low testosterone vary with the definition used, the population studied, and method of analysis used. It was estimated in the Massachusetts Male Aging Study that approximately 6% of 40–69-year-old US men have symptomatic testosterone deficiency.[19] Prevalence estimates from other studies that did not consider signs and symptoms varied from 10% to 25% of the general population.[19–22] Prevalence of hypogonadism in men with COPD also varied among studies, ranging from 22% to 69%.[3,7,11,22,23]

Kamischke et al.[23] reported 69% hypogonadism in their study. Debigare et al.[3] reported that 10 of 45 (22%) patients were hypogonadal. Monique Van Vliet et al.[22] reported that (52%) of their patients had hypogonadism. Laghi et al.[7] reported a percentage of (38%) hypogonadism in their study. This difference may be explained by ethnic factors or due to difference in patients' selection.

COPD patients had significantly lower levels of FSH and LH compared to control group ($p = 0.002$, $r = 0.243$ and $p = 0.001$, $r = 0.351$) respectively. Out of the 50 COPD patients, 22 (73%) showed low levels of FSH and LH. This can be explained by impaired function of the hypothalamic – pituitary gonadal axis in patients with COPD. These results are matching with the results obtained by Laghi et al.[7] who reported that (76%) of the hypogonadal COPD patients had hypo gonadotrophic hypogonadism. These findings can be explained by an impairment of the release of the hypothalamic hormones, malfunction of the released hormones, loss of feedback control mechanism, or a combination of all of them. Some other mechanisms, including chronic disease, hypoxemia, glucocorticoid therapy, and obesity can cause hypo gonadotrophic hypogonadism.[22,24–26]

The remaining 8 patients showed picture of testicular dysfunction. These results are compatible with results of Laghi et al.[7] who reported testicular dysfunction in quarter of their patients. This can be explained by atrophy of Leydig cells,[27] circulating cytokines,[28,29] and use of steroids.[29,30]

SHBG was significantly higher in COPD group compared to control group. Despite the fact that aging has been shown to increase the circulating SHBG concentrations, the age was similar in both COPD and control groups so it cannot explain the increase in SHBG. This may therefore be explained by the low circulating free testosterone concentrations encountered in the COPD patients.[22]

In our study, serum total testosterone level showed a significant positive correlation with both FEV1 and FEV1/FVC ratio ($p = 0.031$ and 0.003 respectively). Serum free testosterone level showed a significant positive correlation with FEV1 ($p = 0.032$). E_2/T ratio was negatively correlated with FEV1 ($p = 0.022$). This significant correlation between the testosterone levels and the severity of airway obstruction further supports the fact that the high prevalence of hypogonadism in COPD patients is related to the pathogenesis of the disease and is different from the late-onset hypogonadism that occurs in the general population. Chronic illnesses such as diabetes mellitus, CVD and hypertension have been associated with a decline in serum testosterone. COPD is a chronic illness and hence may manifest testosterone deficiency.[31] Our results are similar to Karadag et al. who studied a group of stable COPD and patients in an exacerbation and found that Testosterone and DHEAS levels were lower in severe COPD (FEV1 less than 50%) and detected a positive correlation between testosterone and FEV1. Makarevich et al.[10] assessed relation of sex hormone status and the stage of COPD. They concluded that the intensity of sex hormone changes was correlated with the stage of COPD. As the severity of disease increased, testosterone decreased while LH, FSH increased in compensation. Also, Shaker et al. who studied the sex hormones level in COPD patients during exacerbation and after 1 m found that the low levels of serum testosterone found in these patients was significantly correlated to the severity of airway obstruction as measured by FEV1%.[32]

However, other studies have failed to report similar associations as Laghi et al.[7] and Van Vliet et al.[22] who found no relationship between free testosterone level and degree of airflow limitation (FEV1), this could be due to different patients' selection criteria or presence of other comorbidities.

In the present study, Quadriceps muscle force was significantly lower in COPD patients than in the control group ($p = 0.001$). Moreover, the exercise capacity (6-min walk distance) was significantly less in COPD patients than the control group ($p = 0.003$). These results are consistent with previous reports.[22] The mechanisms of skeletal muscle dysfunction in COPD patients could be explained by physical inactivity,[33,34] chronic low-grade systemic inflammation,[22] malnutrition, medication, age, hypoxemia and smoking.

Our results showed that there was no correlation between serum testosterone level and quadriceps muscle force or with exercise capacity (6-min walk distance) in patients with COPD. These results are similar to previous studies.[3,9] For instance, Debigare and associates (3) reported that the prevalence of hypogonadism among men with COPD is equivalent among patients with and without muscle wasting. Similarly, Laghi et al. found that quadriceps strength (and endurance) were similar in hypogonadal and eugonadal men with COPD. In their study, Van Vliet et al.[22] found a significant correlation between testosterone concentrations and quadriceps strength. This finding added more confusion to the available conflicting results.[2,22,35,36] The explanation of these contradictory results regarding the effect of hypodonadism on muscle weakness is not clear; moreover the studies who found a correlation between the testosterone level and the degree of muscle weakness did not show a high statistical significance that could be of clinical importance.[9]

Inflammatory markers levels including hs-CRP and IL-6 were significantly higher in COPD patients compared to control group ($p < 0.001$). Numerous studies performed in recent years provide overwhelming evidence of COPD as a condition characterized by an abnormal inflammatory response beyond the lungs with evidence of low-grade systemic inflammation.[37–41] Raised levels of acute phase proteins like CRP, fibrinogen and pro-inflammatory cytokines such as IL-6 were found in circulation of stable COPD patients[38] and have been shown to be associated with impaired functional capacity,[42] reduced daily physical activity[43] and decreased health status.[40,44]

In our study we found a significant correlation between the inflammatory markers (hs-CRP and IL6) and the severity of airflow obstruction ($p = 0.037$ and 0.002 respectively). It is well established now that systemic inflammation is present in stable COPD patients and that its intensity is related to the severity of the underlying disease.[37–40] Moreover, we found that CRP was inversely correlated with the quadriceps strength as measured by the one repetition maximum as well as the exercise capacity as measured by the 6 min walk distance $P = 0.021$ and $p = 0.036$) respectively, also we found that IL6 was inversely correlated to quadriceps strength ($P = 0.008$). Our results indicate that systemic inflammation in COPD predisposes to skeletal muscle weakness and exercise intolerance in stable COPD patients. In consistence with our results, Yende et al. in their study[45] on 2273 elderly individuals, where the pulmonary function testing revealed that 12% of them had COPD, found that the degree of airflow obstruction, as measured by the FEV_1, was significantly

associated with the degree of muscle weakness. They also found that systemic inflammation as measured by the level of IL-6, was more in patients with COPD and was related to airflow obstruction, muscle weakness and exercise intolerance.

Also Broekhuizen et al.[46] studied 102 patients with severe to very severe COPD, nearly 33% of which were on systemic corticosteroids, who were admitted to an inpatient pulmonary rehabilitation center. They found that reduced FEV_1 was correlated with increased plasma levels of CRP and IL-6, confirming that the severity of airflow limitation is associated with systemic inflammation. Their results are in concordance with previous results showing that raised CRP levels were associated with diminished muscle strength, reduced exercise endurance, workload, 6 min walk distance, and poor health status and quality of life.

Systemic inflammation has been suggested as a possible cause of hypoandrogenemia in male patients with COPD. However, until now, only a weak significant inverse relationship between the circulating levels of IL-6 and bioavailable testosterone has been found in COPD male patients ($r = 0.33$).[3] In the present study we found no significant correlation between the low testosterone and markers of systemic inflammation (hs-CRP and IL-6). Our results are similar to Karadag et al.[47] who studied 103 COPD patients for sex hormone alterations along with inflammatory markers (TNF-α and IL-6). The study group comprised stable COPD patients and patients undergoing a COPD exacerbation. Although sex hormones were lower and circulating IL-6 and TNF-α concentrations were higher in both stable and exacerbation phase COPD groups than controls, there was no correlation between sex hormones and TNF-α or IL-6. Hence, there is no current evidence to support inflammation as a contributor to testosterone deficiency in COPD.

In conclusion hypogonadism is highly prevalent in clinically stable COPD patients and is particularly related to the severity of the airway obstruction. Therefore, regular screening COPD patients for the sex hormone level seem justified. Furthermore, we confirmed that systemic inflammation exists in stable COPD and that the intensity of the inflammatory process relates to the severity of the underlying disease and that systemic inflammation in COPD is a risk factor for peripheral muscle weakness and reduced exercise tolerance. However, we failed to find a significant association between hypogonadism and muscle weakness or systemic inflammation. Future research in this area is needed to shed more light on this matter especially on the role of testosterone replacement therapy in the prevention of hypogonadism and in delaying muscle weakness in COPD patients. Moreover, further investigations could be done to study the effect of other parameters on the occurrence of hypogonadism and the degree of muscle weakness in these patients for example the degree of hypoxemia or hypercapnea as well as electrolyte disturbance and serum uric acid levels.

Declaration of interest

I declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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