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ORIGINAL RESEARCH

The Effect of the Severity of Chronic Obstructive Pulmonary Disease on the Pituitary Gonadal Axis

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ABSTRACT

This study aims to investigate the levels of anabolic hormone implicated in specific clinical symptoms of chronic obstructive pulmonary disease (COPD) in relation to disease severity. Sixty-four male patients with COPD for at least two years were included. COPD diagnosed was based on pulmonary function tests, with severity classified using the CAT score and mMRC breathlessness scale. Levels of various hormones including TSH T3 T4, FSH, LH, testesterone, prolactin, progesterone and CRP were measured. Arterial blood gases were also analyzed. Patients were categorized according to GOLD stages. LH, FSH levels decreased during exacerbation, with a significant positive correlation between LH and low arterial oxygen levels. lower testosterone levels were statistically significant in severe COPD patients with $FEV_1 < 50\%$. A decrease in LH, testosterone FSH, TSH, progesterone and prolactin was observed with low blood oxygen levels, indicating dysfunction in the hypothalamic-pituitary-gonadal axis. However,stastistical significance varied.In conclusion, hormonal changes occur in male COPD patients, particulary related to disease severity. Testesterone levels correlate significantly with COPD severity. LH decrease during pronounced hypoxemia period was notable. Further research is necessary to evaluate the safety and efficacy of testosterone supplementation in COPD patients.

Keywords: Chronic Obstructive Pulmonary Disease. Hormones. Pulmonary Function Test.

Kronik Obstrüktif Akciğer Hastalığının Şiddetinin Hipofizer Gonadal Aks Üzerine Etkisi

ÖZET

Bu çalışmanın amacı, kronik obstrüktif akciğer hastalığının (KOAH) spesifik klinik semptomlarında rol oynayan anabolik hormon düzeylerinin hastalığın şiddeti ile olan ilişkiyi araştırmaktır. En az iki yıldır KOAH'lı altmış dört erkek hasta çalışmaya dahil edildi. KOAH, akciğer fonksiyon testlerine dayanarak teşhis edildi ve şiddeti CAT skoru ve mMRC nefes darlığı ölçeği nefes darlığı ölçeği kullanılarak sınıflandırıldı. TSH T3 T4, FSH, LH, testosteron, prolaktin, progesteron ve CRP dahil olmak üzere çeşitli hormonların seviyeleri ölçüldü. Ayrıca arteriyel kan gazları analiz edildi. Hastalar GOLD evrelerine göre kategorize edildi. LH, FSH seviyeleri alevlenme sırasında azaldı ve LH ile düşük arteriyel oksijen seviyeleri arasında anlamlı pozitif bir korelasyon vardı. FEV1 <%50 olan şiddetli KOAH hastalarında daha düşük testosteron seviyeleri istatistiksel olarak anlamlıydı. LH, testosteron FSH, TSH, progesteron ve prolaktinde bir azalma gözlendi ve düşük kan oksijen seviyeleri gözlendi ve bu hipotalamus-hipofiz-gonadal eksende disfonksiyona işaret ediyordu. Ancak istatistiksel anlamlılık bulunmadı. Sonuç olarak, erkek KOAH hastalarında hormonal değişiklikler meydana gelir, özellikle hastalığın şiddetiyle ilişkilidir. Testesteron seviyesi KOAH şiddeti arasında istatistiksel olarak anlamlı ilişki tespit edildi. Hipokseminin daha belirgin olduğu dönemde LH azalması dikkat çekiciydi. KOAH hastalarında testesteron takviyesinin güvenliğini ve etkinliğini değerlendirmek için daha fazla araştırma gereklidir.

Anahtar Kelimeler: Kronik Obstrüktif Akciğer Hastalığı. Hormonlar. Akciğer Fonksiyon Testi.

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Chronic obstructive pulmonary disease (COPD) is a prevalent and treatable condition characterized by chronic inflammation in the airways (bronchitis, bronchiolitis) and and/or alveoli (emphysema), often leading to progressive permanent airflow obstruction[1]. This inflammation leads to progressive airway narrowing and lung tissue damage. Studies suggest that COPD is projected to become the fourth leading cause of death by 2030. The presence of comorbidities exacerbates the severity of COPD, necessitating increased healthcare interventions[2,3].

COPD not only affects the respiratory system but also influences various systemic functions, including endocrine organs. thyroid function alterations may occur in COPD patients due to factors such as hypoxia and airway obstruction.[4]

Some researchers have suggested dysfunction in the hypothalamic-pituitary-gonadal axis in COPD patients. However, it is essential to note that these changes cannot be solely attributed to COPD, as factors like hipoxia, disease severity, smoking habits, corticosteroid use, and underlying inflammatory conditions can also contribute to decreased testosterone levels.[5]

The current study aimed to explore the correlation between pituitary and gonadal hormonal levels and the severity of COPD in patients attending a chest diseases outpatient clinic.

Material and Method

Place and Time of the Study

The research was conducted at the Chest Diseases Polyclinic of the University of Health Sciences, Mehmet Akif İnan Training and Research Hospital between November 2022 and June 2023.

Study Population and Sample

The study population consisted of patients diagnosed with COPD who visited the Mehmet Akif İnan Training and Research, Hospital Chest Diseases Outpatient Clinic during the specified period. Approval was obtained from the ethics committee (no. HRU/22.21.12) on October 31,2022. Inclusion criteria encompassed patients diagnosed with COPD for a minimum of two years who provided informed consent. Our research is a prospective study. Exclusion criteria consisted of patients with respiratory diseases other than COPD and those taking medications affecting the endocrine system, metabolism, renal, hepatic, rheumatic, and hormonal metabolism. Demographic data including age, disease duration, body mass index (BMI), clinical information, home oxygen use, comorbidities, and smoking history, were collected through face-to-face interviews and medical records review. Chest X-rays, pulmonary function test (PFT) and arterial blood gas analyses were conducted. COPD severity was determined based on FEV1 values.

Diagnosis of COPD was confirmed through chest radiography and pulmonary function tests with COPD defined as a FEV/$_1$FVC ratio below 70% s COPD severity was stratified into Very Severe (FEV1 < 30%). Severe (FEV_1 50-30%) Moderate (FEV1 50-80 %) and Mild (FEV1>%80) stages. Disease severity was assessed using the COPD Assessment Test (CAT) score, and the Modified Medical Research Council (mMRC) dispnea scale and pulmonary function test (PFT). Blood tests were taken from the patients in the morning.

Levels of serum TSH, T3, T4, FSH, LH, progesterone, prolactin, CRP, and testosterone were measured via radioimmunoassay.

The relationship between COPD severity classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification, and levels of luteinizing hormone (LH), triiodothyronine (T3), thyroxine (T4), follicle stimulating hormone (FSH), and testosterone was analyzed using appropriate statistical methods. Hormonal and biochemical markers, including prolactin, FSH, LH, testosterone, progesterone, TSH, T3, T4, and C-reactive protein (CRP), were determined using radioimmunoassay techniques. Arterial blood gas analyses were performed after a 30- minute rest in ambient air to measure partial oxygen (oxygen (PaO_2 mmHg) and partial carbon dioxide ($PaCO_2$ mmHg) levels as well as PH values

Statistical Analysis

Statistical analysis was conducted using SPSS 22.0 (IBM, Chicago, USA). Normality of data distribution was assessed through visual and analytical methods. Descriptive statistics were presented as mean standard deviation for normally distributed continuous variables, median(minimum-maximum) for non-normally distributed variables, and numbers with percentages for categorical data. The relationship between FEF 25-75 and testosterone in COPD patients has changed in Pearson correlation test. A comparison was made between the stages of COPD patients and their hormonal values. The Mann-Whitney u test and Wilcoxon signed Rank test were employed for non-normally distributed variables, with statistical significance set at $p < 0.05$.

Results

The study included 64 patients with a mean age of 65.45 ± 79 years Whose severity of COPD were categorized according to the GOLD classification.

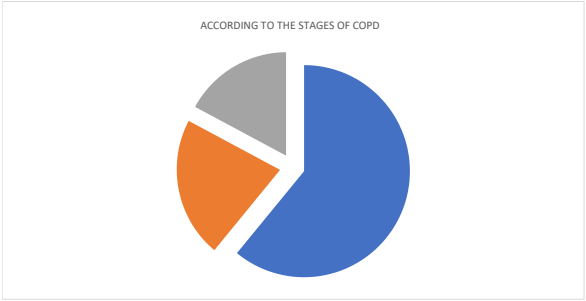
A significant negative correlation was observed between smoking history (pack/year) and serum testosterone levels, indicating a decline in testosterone levels with increasing COPD severity. However, no statistically significant association was found between age and COPD severity. While a relationship was noted between serum FSH levels and COPD severity, it was not statistically significant.

The study found no statistically significant association between COPD severity and serum T3 or T4 levels. Although a trend of decreasing T3 and T4 levels with increasing COPD severity was observed, it was not

statistically significant. Although an increase in serum CRP levels correlated with COPD severity, this association did not reach statistical significance. Serum LH and prolactin levels showed a positive correlation with COPD severity, although statistical significance was not reached (Table I). According to GOLD stages, the majority of patients were classified as GOLD stage 2 (60,09%) (Figure 1).

Table I. Stage of COPD severity

Parameter	MEDIUM (50-79)	SEVERE (30-49)	Very severe<30	P Value
Patient distribution	19 (30.58)	34 (30.90)	10 (41.90)	0.428
BMI (kg/ m2)	19 (36.66)	34 (30.66)	10 (32.30)	0.597
SMOKER (%)	33.68	32	32	0.016
AGE OF DISEASE (%)	33.63	31.15	32.30	0.484
ADDITIONAL DISEASE	36.89	31.94	24.6	0.063
LH (mIU/ml)	8.2±4.9	8.6±4.43	10.56±5.1	0.114
FSH	9.53±7.33	9.38±7.11	7.95±4.23	0.709
PROLACTIN (ng/ml)	9.46±4.43	11.88±7.94	14.95±7.71	0.324
PROGESTERON	0.20±0.177	0.15±0.07	0.16±0.11	0.513
TESTESTERONE (ng/ml)	4.36±2.07	4.23±1.77	3.83±1.47	0.018
TSH	1.87±0.58	2.03±2.11	2.21±1.39	0.153
T3	5.06±0.77	4.80±0.71	4.38±0.60	0.140
T4	16.59±2.75	15.76±3.18	15.70±2.21	0.642
CRP	8.80±16.79	12.89±22.20	13.94±19.98	0.074



GOLD Stage 2 %60,09, GOLD Stage 3 % 21,87%, GOLD Stage 4 %17,18

Figure 1.
Distribution according to COPD GOLD Stages

No statistical difference was found between FEF 25-75 and testosterone(p 0= .511).

Arterial blood gas analysis revealed a statistically significant association between low PaO2 levels (55 < 55mmHg) and decreased LH levels. However, no statistically significant association were found between PaO2 levels and other hormonal markers such as testosterone, FSH, TSH, progesterone, prolactin, and CRP, nor with T3 or T4 levels (Table II)

Table II. Arterial blood gas oxygen ratios of COPD patients

Parameter	PaO2 above 55mmHg	PaO2 below 55 mmHg	P Value
LH	10.78 ±5.64	7.77±3.75	0.610
FSH	10.25±8.25	8.65±5.77	0.936
Testosterone	4.32±1.80	4.18±.1.81	0.042
Progesteron	0.18±0.09	0.16±0.12	0.455
Prolactin	13.18±7.15	10.86±7.07	0.266
TSH	2.03±1.37	1.99±1.81	0.903
T3	4.58±0.71	4.92±0.72	0.127
T4	15.81±2.87	16.23±3.06	0.159
CRP	10.59±14.33	12.22±22.68	0.867
Mean Age	67.29±7.67	64.57±7.86	0.327

According to the arterial blood gas studies of the patients, it was found statistically significant that LH was found to be low in patients with a low PaO2 value of 55 mmHg. Although testosterone, FSH, TSH, progesterone, prolactin and progesterone levels were found to be low and CRP, T3, T4 levels were found to be high in patients with arterial blood gases with PaO2 lower than 55mmHg, it was not statistically significant (Table II).

Discussion and Conclusion

COPD is know to exert systemic effects beyond the respiratory system, affecting various endocrine organs including the pituitary gland, thyroid, gonads adrenals, and pancreas. While the precise mechanisms underlying the impact of COPD on the endocrine system remain incompletely understood, factors such as hypoxemia, hypercapnia, system inflammation, and glucocorticoid therapy are believed to contribute to these alterations.[5,6]

Dysfunction of the hypothalamic-pituitary-gonadal axis has been frequently reported in COPD patients. Several studies investigating sex hormone status in COPD patients have implicated hypoxia, disease severity, smoking, corticosteroid therapy, and underlying these changes remain to be fully elucidated.[5]

Our study cohort predominantly consisted of COPD patients who had been using inhaled corticosteroids with β2 agonist as bronchodilators for at least two years. Previous research has indicated that both intravenous and inhaled steroid administration during exacerbations may contribute to decreased testosterone levels. Choronic wasting syndrome observed in COPD patients has also been associated with reduced levels of anabolic hormones. While numerous studies have reported decreased levels of anabolic hormones in COPD patients the underlying causes remain unclear.[7]

Some investigations have suggested that hypogonadism in choronic diseases is associated with body mass index (BMI), systemic inflammation and oxidative stress, all of which contribute to muscle atrophy and malnutrition in COPD.[8,9] In our study, we found that there was a negative correlation between BMI and severity of the disease in COPD patients included in the study. It was however not statistically significant ($p \geq 0.5$).

Thyroid function in COPD patients has been the subject of limited research, yielding conflicting results. Some studies have reported normal throid hormone levels in COPD patients,while others have noted correlations between throid hormone levels and markers of disease severity such as PaO2.[4,10-14] Our study found decrease in T3 and T4 levels and increase TSH levels as COPD severity increased, although these associations were not statistically significant.

Casaburi et al. reported that gonadal axis was the commonly examined system in COPD patients and the patients in their study were predominantly male.[15] The patients in our study were male COPD patients and all of them were smokers.

Similarly, alterations in gonadal hormone levels have been observed in COPD patients, with testosterone levels decreasing as disease severşty increases. While the precise mechanisms underlying hypogonadism in COPD remain unclear, factors such as hypoxemia, hypercapnia and steroid use have been implicated.[5,15-20]

Akbaş et al. found PRL is the first hormone reported to increase in response to acute physical and psychological stress. In a study conducted in COPD patients, PRL levels of patients were found to be higher than controls[17].

In our study, prolactin level was negatively correlated with FEV1. Low oxygen levels in the blood caused a decrease in LH, testosterone, FSH, TSH, progesterone and prolactin hormones. Although this lowness of level was not statistically significant, it suggests a dysfunction of the hypothalamic-pituitary-gonadal axis.

They showed that the prevalence of hypogonadism increased with COPD severity in men with stable COPD is higher and that COPD severity and testosterone levels were inversely related, with lower free testosterone levels in more severe COPD patients.[21]

They found a higher prevalence of hypogonadism with increasing severity of COPD in men with stable COPD and an inverse correlation between COPD severity and testosterone levels in different studies. They found lower free testosterone levels in patients with more severe COPD.[21-23]

We found in our study that there was an inverse relationship between the progression of COPD stage and the decrease in testosterone levels in 64 male patients and this relationship between COPD stages and testosterone levels was found statistically significant ($p<0.5$).

Similar studies, the relationship between COPD severity and CRP has been evaluated. CRP is an acute phase protein synthesized primarily from liver cells in response to inflammation and tissue damage. They showed that the increase in CRP level in COPD attack and stable period is directly related to COPD and systemic inflammation accompanying COPD and also secondary to smoking.[24-28] In our patients, CRP level was with severity of COPD. CRP was level high in COPD patients with oxygen pressure lower than 55mmHg. The values were not significant. ($p \geq 0.5$).

In our study, we noted a decline in testosterone levels correlating with the escalating severity of COPD. We found a positive correlation between the patient's FEV_1. This relationship was statistically significant ($p<0.5$). We observed that our research coincided with the study in the literature.

In conclusion our study provides further evidence of alterations in pituitary hormone levels in male COPD patients, particularly in relation to disease severity and markers such as FEV1 and hypoxemia. These hormonal changes likely result from a complex interplay of factors, including hypoxemia, systemic inflammation, and corticosteroid therapy. According to GOLD stages, stage 2 was 60.09%, stage 3 was 21.87%, stage 4 was 17.18%.

The distribution of COPD severity by group in our study was predominantly GOLD stage 2 (Figure 1).

We observed significant variations in hormone levels according to FEV1 levels, suggesting a direct association between COPD severity and hormone alterations. Our findings align with previous studies in the literature, highlighting the importance of assessing hormonal status in COPD patients.

Given the observed decline in testosterone levels in severe COPD patients, testosterone supplementation may represent a potential therapeutic avenue. However, further studies are warranted to evaluate the safety, optimal duration, and dosage of testosterone replacement therapy in COPD patients.

In summary, our study underscores the importance of understanding the endocrine alterations in COPD patients and suggests the need for comprehensive hormonal assessments as part of COPD management strategies.

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