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Hypogonadism in chronic obstructive pulmonary disease (COPD) – risk factors

Hipogonadizam u hroničnoj opstruktivnoj bolesti pluća (HOBP) – faktori rizika

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Abstract

Bacground/Aim. Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality in pulmonary pathology. However, apart from its own pulmonary manifestations, this disease is also characterized by systemic effects, including hypogonadism which is described especially in the group of men with COPD. The aim of this study was to evaluate risk factors for hypogonadism in men with COPD. **Methods.** The study included 96 male patients with COPD in stable phase of the disease. All patients were checked for concentration of free testosterone in serum, markers of systemic inflammation, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and C reactive protein (CRP), pulmonary function test, gas exchange parameters, a 6-minute walk test (6MWT), nutritional status and condition of skeletal muscle (midthigh muscle cross-sectional area – MTCSA using computed tomography). **Results.** Decreased value of free testosterone was found in 37.5% of the patients. In the group with hypogonadism (free testosterone < 4.5 pg/mL), we found significantly increased serum concentration of TNF-α (5.88 ± 3.21 vs. 3.16 ± 2.53 pg/mL; $p < 0.05$), significantly lower MTSCA (68.2 ± 18.72 vs. 91.1 ± 21.4 cm^2; $p < 0.05$) and the 6MWT (268.33 ± 32.35 vs. 334.25 ± 43.25 m; $p < 0.05$). Lung function, gas exchange markers and body mass index (BMI) were similar in both groups. The multivariate regression analysis singled out serum value of TNF-α as an independent predictor of serum concentrations of free testosterone (B = -0.157; 95% confidence interval: -0.262–0.053). **Conclusion.** In our analysis we found that TNF-α as a marker of systemic inflammation is an independent predictor of the presence of hypogonadism in the patients with COPD. Our results indicate that hypogonadism predisposes to skeletal muscle wasting and exercise intolerance in male COPD patients.

Key words:
hypogonadism; pulmonary disease, chronic obstructive; risk factors.

Apstrakt

Uvod/Cilj. Hronična opstruktivna bolest pluća (HOBP) je vodeći uzrok morbiditeta i mortaliteta u plućnoj patologiji. Osim plućnih manifestacija, HOBP karakterišu brojni sistemski efekti, među kojima je opisan i hipogonadizam posebno u grupi muškaraca sa ovom bolešću. Cilj studije bio je procena faktora rizika za pojavu hipogonadizama kod muškaraca sa HOBP. **Metode.** Istraživanjem je obuhvaćeno 96 bolesnika muškog pola sa HOBP u stabilnoj fazi bolesti. Kod svih bolesnika određena je koncentracija: slobodnog testosterona u serumu, markera sistemske inflamacije, faktora nekroze tumora-alfa (TNF-α), interleukin 1-beta (IL-1β) i C-reaktivnog proteina (CRP), izvršeno je ispitivanje plućne funkcije, parametara gasne razmene, 6-minutni test hoda (6MWT), stanje uhranjenosti i stanje skeletnih mišića (*midthigh muscle cross-sectional area* – MTCSA), pomoću kompjuterizovane tomografije). **Rezultati.** Zastupljenost ispitanika sa hipogonadizmom je bila 37.5%. Ispitanici sa hipogonadizmom (slobodan testosteron < 4,5 pg/mL) su imali značajno povećanu koncentraciju TNF-α u serumu (5,88 ± 3,21 vs. 3,16 ± 2,53 pg/mL; $p < 0,05$), značajno manji MTSCA (68,2 ± 18,72 vs. 91,1 ± 21,4 cm^2; $p < 0,05$) i 6MWT (268,33 ± 32,35 vs. 334,25 ± 43,25 m; $p < 0,05$). Nije ustanovljena statistički značajna razlika između ove dve grupe ispitanika u pogledu starosti, parametara plućne funkcije i gasne razmene, kao i indeksa telesne mase. Pomoću multivarijantne resgresione analize kao nezavisni prediktor koncentracije slobodnog testosterona izdvojila se serumska vrednost TNF-α (B= -0.157; 95% interval poverenja: -0.262–0.053). **Zaključak.** Analizom je ustanovljeno da TNF-α, kao sistemski marker inflamacije, predstavlja nezavisni prediktor za postojanje hipogonadizma kod bolesnika sa HOBP. Hipogonadizam je značajno povezan sa gubitkom mišićne mase i lošijim tolerisanjem napora kod ovih bolesnika.

Ključne reči:
hipogonadizam; pluća, opstruktivna bolest, hronična; faktori rizika.

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Introduction

Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality in pulmonary pathology. However, apart from its own pulmonary manifestations, this disease is also characterized by systemic effects which are reflected in other tissue damage [1]. The COPD patients with progressive disease develop hypoxaemia and hypercapnia and systemic inflammation which can, along with the use of chronic glucocorticoid therapy, result in hypogonadism [2]. Previous investigations showed that male patients with COPD could develop hypogonadism and there was evidence that these patients had significant atrophy of Leydig cells. It was observed that many patients with COPD, most of whom are middle-aged or elderly, fit the profile of late-onset hypogonadism manifested by diminished energy level, libido and loss of skeletal muscle mass [3, 4]. One study showed that 75% of male COPD patients with low level of serum testosterone also had a low level of gonadotropine (secundary hypogonadism), while at the remaining 25% increased gonadotropine level (primary hypogonadism) was noticed [5].

Recent studies on male COPD patients have implied that hypogonadism could contribute to development of skeletal muscle dysfunction. Physical inactivity – sedentary lifestyle in patients with advanced chronic obstructive pulmonary disease (COPD) leads to weakening of muscles of lower extremities, especially quadriceps which is closely related to atrophy of muscles of thigh region [6].

The primary aim of this study is to assess the potential risk factors for hypogonadism in male COPD patients in stable state of the disease.

Methods

This clinical, cross-sectional study was conducted at the Clinic for Pulmonology, Clinical Centre Kragujevac, from January 2015 to June 2016. The protocol study was approved by the local Ethics Committee and written informed consent was obtained from each patient.

Subjects

The study included 96 male COPD patients in stable phase of the disease. All included patients fulfilled criteria for the COPD diagnosis according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) and they were in stable phase of the disease (without systemic corticosteroid therapy in last 4 weeks).

Exclusion criteria were: patients unable to perform lung function testing and a 6-minute walking test, patients with myocardial infarction within last 4 months, patients with unstable angina pectoris or heart failure NYHA III and IV as well as patients with history of primary or secondary hypogonadism, alcohol consumers and those with chronic kidney disease.

Laboratory assessments

Blood samples were taken by cubital venipuncture in the morning. Then, sex hormone was measured.

To measure the concentration of free serum testosterone for hypogonadism estimation, immunohistochemistry method (enzyme-linked immunosorbent assay – ELISA technology) was used (Nova Tec Immunodiagnostica Gmbh, Dietzenhbach, Germany). Cut off value for normal free serum testosterone was ≥ 4.5 pg/mL. Based on that value, the patients were divided into 2 groups: one with the value of free testosterone ≥ 4.5 pg/mL (normal value) and one with serum free testosterone below 4.5 pg/mL (decreased value). Systemic inflammation markers were serum concentration of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) which were measured by immunochemistry method (ELISA technology) (Orgenium, Helsinki, Finland) and C reactive protein (CRP).

Pulmonary function tests

All patients underwent standard spirometry testing before and after bronchodilator inhalation. The lung function testing was done by spirometer (Master Screen Pneumo Jaeger, Germany). Forced vital capacity (FVC), forced expirium volume in the first second (FEV1) and FEV1/FVC ratio were measured. The subjects who had postbronchodilatatory FEV1/FVC < 0.70 were classified into 4 COPD severity groups based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: FEV1 ≥80% of predicted (GOLD 1: mild stage), 50% ≤ FEV1 < 80% of predicted (GOLD 2: moderate stage), 30% ≤ FEV1 < 50% of predicted (GOLD 3: severe stage), FEV_1 < 30% of predicted (GOLD 4; very severe stage).

Body plethysmography (Master Screen Body Jaeger, Germany) was used to measure the total pulmonary capacity (TLC), thoracic gas volume at the end of calm expirium (TGV), residual volume (RV) and RV/TLC ratio.

Nutritional status

Nutritional status was determined according to the body mass index (BMI) calculated as body mass expressed in kilograms divided with squared body height expressed in meters. Undernutrition is defined as BMI < 18.5kg/m², normal nutrition is defined as BMI = 18.5–24.9 kg/m², overnutrition is defined as BMI = 25–29.9 kg/m² and obesity is defined as BMI > 30 kg/m².

Six-minute walking distance

Six-minute walking test (6MWT) was performed for exercise tolerance estimation. The test was performed on 30 meters distance and the total distance passed was expressed in meters (m).

Skeletal muscle condition

Area of cross-section of right femur muscles (*midthigh muscle cross-sectional area* – MTCSA) in the middle of the distance between pubic symphysis and femur condyle was measured by computed tomography (CT) in all patients (CT-Toshiba Scanner TSX101A). MTCSA density within values of 40–100 HU was determined by measuring this tissue area. MTCSA less than 70 cm² was considered to be a decreased value of cross-sectional area of the right femur muscle. All pictures were analyzed by one (blinded) investigator.

Statistical analysis

Descriptive statistic methods of middle values (arithmetic average, mediana), variability values (standard deviation, interval of variation, minimal and maximal value) and structure indicator (presented as percentage) were used. Significance of difference of continual data was tested with the *t*-test for 2 independent samples and with the Mann-Whitney U test and Wilcoxon signed rank test. Significance of difference frequency of categorical data was tested with the Fisher accurate probability test. The linear regression analysis was used to examine the relationship between free testosterone and the test scores, lung function, and 6 MWD. Using multivariate regression analysis, we examined the influence of the individual variables as independent predictors for observed parameters. Data were worked out in the SPSS (Statistical Package for Social Sciences)19.0 program.

Results

In this study, 96 male patients with stable COPD were investigated. The average age was 68.8 ± 9.64 years (range 57 to 79 years). Twenty-eight (29.2%) patients were current smokers. Thirty-six (37.5%) patients had mild and moderate COPD, 36 (37.5%) severe and 24 (25.0%) patients suffered from very severe COPD (Table 1).

Table 1

Demographics characteristics, GOLD study, inflammatory markers, MTCSA and 6MWT in the study group (n = 96)

Characteristics	Values
Age (years), mean ± SD	68.82 ± 9.64
BMI (kg/m²), mean ± SD	21.7 ± 2.35
Smoking habits, n (%)	
current smoker	28 (29.2)
ex-smoker	68 (70.8)
COPD stage, n (%)	
GOLD 1 and 2	36 (37.5)
GOLD 3	36 (37.5)
GOLD 4	24 (25.0)
Inflammatory markers, mean ± SD	
CRP (mg/L)	6.81 ± 8.61
TNF-α (pg/mL)	4.45 ± 2.55
IL-1β (pg/mL)	184.49 ±56.54
MTCSA (cm²)	86.92 ± 14.5
6MWT (m)	302.2 ± 24.23

BMI – body mass index; COPD – chronic obstructive pulmonary disease; GOLD – global initiative for chronic obstructive lung disease; CRP – C reactive protein; TNF-α – tumor necrosis factor-α; IL-1β – interleukin-1β; MTCSA – midthigh muscle cross-sectional area; 6MWT – six-minute walking test; SD – standard deviation.

Tabele 2

Characteristics of the patients in the groups with low and normal value of free testosterone

Variable	Free testosterone		*p*
	< 4.5pg/mL	≥ 4.5pg/mL	
COPD patients, n (%)	36 (37.5)	60 (62.5)	
Age (years), mean ± SD	68.50 ± 7.69	67.83 ± 9.42	0.315
BMI (kg/m²), mean ± SD	20.7 ± 3.8	23.7 ± 6.4	0.138
Smoking habits, n (%)			
current smokers	10 (27.8)	18 (30.0)	0.871
ex-smokers	26 (72.2)	42 (70.0)	0.753
Lung function parameters, mean ± SD			
FVC (%)	56.65 ± 37.71	61.06 ± 32.80	0.362
FEV1 (%)	37.60 ± 17.91	37.88 ± 20.29	0.438
FEV1/FVC	45.52 ± 8.13	42.72 ± 16.98	0.713
TLC (%)	123.25 ± 23.82	117.15 ± 43.09	0.227
TGV (%)	191.48 ± 50.34	170.93 ± 80.87	0.093
RV (%)	237.38 ± 72.71	198.75 ± 110.53	0.068
RV/TLC	69.19 ± 15.46	60.83 ± 21.97	0.348
Parameters of gas exchange (mmHg), mean ± SD			
PaO2	8.99 ± 2.02	8.05 ± 1.52	0.440
PaCO2	6.15 ± 1.52	6.58 ± 1.81	0.287
COPD stage, n (%)			
GOLD 1 and 2	12 (33.3)	24 (40.0)	
GOLD 3	14 (38.9)	22 (36.7)	
GOLD stage 4	10 (27.8)	14 (23.3)	
Inflammatory markers, mean ± SD			
CRP (mg/L)	7.2 ± 6.21	7.71 ± 9.71	0.322
TNF-α (pg/mL)	5.88 ± 3.21	3.16 ± 2.53	0.021*
IL-1β (pg/mL)	195.9 ± 87.73	195.56 ± 62.70	0.452
MTCSA (cm²)	68.2 ± 18.72	91.1 ± 21.4	0.014*
6MWT (m)	268.33 ± 32.35	334.25 ± 43.25	0.023*

χ^2 test; * statistically significant.

BMI – body mass index; FVC – forced vital capacity; FEV1 – forced expirium volume in the first second; FEV1/FVC – forced expirium volume in the first second/forced vital capacity ratio; TLC – total pulmonary capacity; TGV – thoracic gas volume at the end of calm expirium; RV – residual volume; RV/TLC – residual volume/total pulmonary capacity ratio; PaO2 – partial pressure of oxygen; PaCO2 – partial pressure of carbon dioxide; COPD – chronic obstructive pulmonary disease; GOLD – global initiative for chronic obstructive lung disease; CRP – C reactive protein; TNF-α – tumor necrosis factor-α; IL-1β – interleukin-1β; MTCSA – midthigh muscle cross-sectional area; 6MWT – six-minute walking test; SD – standard deviation.

The average free testosterone value in the study group was 13.99 ± 20.89 pg/mL (range 0.45 to 96.45 pg/mL). We found a low value of free testosterone (< 4.5 pg/mL) in 36 (37.5%) patients. According to the value of free testosterone, the patients were divided into 2 age matched groups (Table 2).

There was not statistically significant difference between parameters of lung function. We found that the value of free serum testosterone and a stage of COPD were independent (χ^2; $p = 0.177$).

Analysis of systemic inflammatory markers between groups showed significant difference only for serum values of TNF-α (Table 2). The patients with the low value of serum free testosterone had significantly lower mean value of MTCSA and distance traveled during the 6MWT.

Using the univariate and multivariate linear regression analysis, we examined the influence of individual variables as independent predictors of the free testosterone value (Table 3 and 4). The multivariate regression analysis singled out the serum value of TNF-α as an independent predictor of free testosterone concentration in serum in the male COPD patients.

Table 3

Univariate Analysis of Risk Factors Related to plasma level of free testosterone

The observed risk factors	Univariate regression analysis	
	#B (95% CI)	*p*
Age (years)	0.089 (0.021–0.199)	0.109
BMI (kg/m²)	3.988 (-0.02–7.995)	0.047*
FEV1 (%)	0.033 (-0.019–0.084)	0.220
TLC (%)	-0.025 (-0.115–0.065)	0.703
RV/TLC	-0.002 (-0.045–0.042)	0.839
PaO2 (mmHg)	0.131 (-0.021–0.284)	0.042*
CRP (mg/L)	-0.184 (-0.386–0.018)	0.303
TNF-α (pg/mL)	-0.192 (-0.284–0.10)	0.01*
Il-1 (pg/mL)	-0.076 (-0.239–0.086)	0.208

#Unstandardized coefficient B; *statistically significant. BMI – body mass index; FEV1 – forced expirium volume in the first second; TLC – total pulmonary capacity; RV/TLC – residual volume/total pulmonary capacity ratio; PaO2 – partial pressure of oxygen; CRP – C reactive protein; TNF-α – tumor necrosis factor-α; IL-1β - interleukin-1β; CI – confidence interval.

Table 4

Multivariate regression analysis of risk factors related to plasma level of free testosterone

The observed risk factors	Multivariate $R^2 = 0.929$	
	B (95% CI)	*p*
BMI (kg/m²)	0.024 (-0.036–0.085)	0.687
PaO2 (mmHg)	1.192 (-1.844–4.229)	0.198
TNF-α (pg/mL)	-0.157 (-0.262–0.053)	0.004

#Unstandardized coefficient B; *statistically significant. BMI – body mass index; PaO2 – partial pressure of oxygen; TNF-α - tumor necrosis factor-α.

Discussion

In our study, 96 men with stable COPD were investigated and subdivided into 2 groups according to the serum free testosterone level (< 4.5 or ≥ 4.5 pg/mL). In the group of patients with the low free testosterone level, a significantly higher value of TNF-α, along with the lower values of MTCSA and 6MWT were found. The level of free serum testosterone and the stage of COPD were found to be independent. TNF-α seems to be an independent predictor of the serum free testosterone level in the COPD patients.

Decreased levels of anabolic hormones have been described in various chronic illnesses, including chronic respiratory diseases. It was shown that many chronic illnesses, such as hypertension, diabetes and cerebrovascular illnesses, are associated with deficit of serum testosterone. Since COPD is also a chronic disease, it can be manifested through the decreased level of serum testosterone – hypogonadism [7].

In our study, we showed that hypogonadism was present in 37.5% of the COPD male patients. Our results are similar to results from Laghi et al. [8] who reported hypogonadism percentage of 38% in their study. Several recently published studies reported that prevalence of hypogonadism in males with COPD varies between 22% and 69% [5]. Significant variations in reported prevalence rates could be explained by the use of different criteria in patient selection, small sample size, the age of patients and their race.

COPD, as well as other chronic illnesses, is characterized by an increased concentration of inflammatory cytokines in circulation which results in a shift of balance towards catabolism with a decrease in anabolic effects [9, 10]. Apart from local inflammation in the airways, the low grade systemic inflammation, caused by the presence of numerous inflammatory cytokines within circulation and high concentration of certain inflammatory mediators on systemic level, was also noticed [11]. The low level of systemic inflammation is considered to be involved in patogenesis of various extrapulmonary disorders, systemic COPD manifestations, including skeletal muscle dysfunction and hypogonadism [12]. TNF-α and other inflammatory cytokines are partially responsible for muscle weight loss and cachexia [12].

The analysis of systemic inflammation markers in our study showed that a statistically significant difference between groups with normal and low values of free testosterone was found only for serum of the TNF-α value. Also, the serum value of TNF-α was found to be an independent predictor of free testosterone. However, Daabis et al. [13] did not find any significant correlation between the low testosterone and markers of systemic inflammation [high-sensitivity C reactive protein (hs-CRP) and interleukin-6 (IL-6)]. Similarly, in the study from Karadag et al. [9] , there was no correlation between sex hormones and TNF-α or IL-6.

Even though systemic inflammation is considered to be a possible cause of decreased level of free testosterone in the COPD male patients, currently, available literature data show no clear evidence to support this theory.

We found no correlation between the free serum testosterone levels and the COPD stages.

Also, no statistically significant lower average value of FEV1 and other parameters of lung function was measured in the group of the COPD patients with low value of free testosterone. Other studies did not show any association between free serum testosterone and the stage of COPD, either [8], [14, 15]. A recent study showed significantly positive correlation between serum free testosterone concentrations and FEV1 [13]. In the group of patients suffering from very severe COPD with the lowest FEV1 value, the testosterone level was lower than in other groups. As the severity of disease increased, testosterone decreased while luteinizing hormone (LH), follicle-stimulating hormone (FSH) increased in compensation. Shaker et al. [16] , who analysed the sex hormones level in the COPD patients during exacerbation and one month after the exacerbation, proved that the low levels of serum testosterone, found in these patients, were significantly correlated with severity of airway obstruction, measured by FEV1.

In the group of patients with the low value of free testosterone, we found the significantly lower values of peripheral muscle mass, evaluated by CT (MTCSA). Previous studies showed that low serum testosterone level could contribute to skeletal muscle dysfunction in the COPD male patients, that is to muscle wasting [14, 17], mainly due to high prevalence of hypogonadism in advanced stages of disease and also due to reduced anabolic effects of testosterone on muscles. However, it could not be claimed that the reduced level of serum testosterone is a key factor in muscle wasting. Muscle wasting with significant protein decomposition is associated with systemic inflammation which is also present in COPD [11]. Increased concentration of inflammatory cytokines in some COPD patients with muscle wasting [11], could be attributed to decreased testosterone secretion and influence on the Leydig cell function [18]. On the other side, anabolic hormones have the tendence to „down regulate“ cytokine expression, so that the reduced testosterone could induce an increase of the inflammatory cytokine IL-6 level, which potentiates its pro-catabolic effect [10, 13, 18]. It seems that there is a regulatory loop in-between the inflammatory cytokines and anabolic steroids [10, 18].

Muscular wasting is frequently encountered in the COPD patients and is related to a decrease in exercise tolerance [19]. Our results showed significant reduction of the exercise tolerance, measured by 6MWT in the COPD patients with hypogonadism. Regarding the fact that significantly lower MTSCA was found in the group of patients with hypogonadism, possible explanation is that hypogonadism contributes to low exercise tolerance in these patients through its influence on muscle wasting. Other studies have not confirmed that there is a relation between reduced exercise tolerance and the level of testosterone [4, 10, 13].

Conclusion

In our analysis we found that TNF-α as a marker of systemic inflammation is an independent predictor of the presence of hypogonadism in the patients with COPD. Our results indicate that hypogonadism predisposes to skeletal muscle wasting and exercise intolerance in the COPD male patients.

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