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ORIGINAL ARTICLE

Prevalence of hypogonadism in men with and without chronic obstructive pulmonary disease: A cross-sectional study

Horacio Matías Castro[a,*], **Pablo Knoblovits**[b], **Joaquin Maritano Furcada**[a], **Eduardo Luis De Vito**[c], **Sebastián Matias Suarez**[b], **Pablo Rene Costanzo**[b]

[a] *Pulmonology Department, Hospital Italiano de Buenos Aires, Argentina*
[b] *Andrology Section, Endocrinology, Metabolism and Nuclear Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina*
[c] *Institute of Medical Research Alfredo Lanari, Faculty of Medicine, University of Buenos Aires, Argentina*

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KEYWORDS
Chronic obstructive pulmonary disease;
Comorbidities;
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Abstract
Background: Hypogonadism is a common finding of chronic obstructive pulmonary disease (COPD). However, the prevalence of hypogonadism in COPD varies among studies. The aim of this study was to determine and compare the prevalence of hypogonadism in men with and without COPD.
Methods: We conducted a cross-sectional study with 134 patients with stable COPD and 70 age-matched men with non-COPD. Hypogonadism was defined by the presence of symptoms according to the Androgen Deficiency in Aging Males questionnaire, along with total testosterone deficiency (<300 ng/dL).
Results: Patients had a mean age of 68 years (SD, 6), a body mass index of 28 kg/m^2 (SD, 6), and 17% were current smokers. The prevalence of hypogonadism was 41.8% in COPD men ($N = 56$, 95%CI, 33–51) and 10.0% in non-COPD men ($N = 7$, 95%CI, 4–20), with a prevalence ratio of 4.2 (95%CI, 2.0–8.7, $p < 0.001$). The prevalence of low total testosterone concentrations (<300 ng/dL) were significantly higher in COPD patients vs the control group (47.0% vs 15.7%, $p = <0.001$). In the COPD group, 89.3% of patients had hypogonadotropic hypogonadism and 10.7%, hypergonadotropic hypogonadism. The prevalence of hypogonadism was higher in severe vs non-severe COPD patients (55.8% vs 35.2%; $p = 0.024$).

Abbreviations: ADAM, Androgen Deficiency in Aging Males; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FSH, follicle-stimulating hormone; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LH, luteinizing hormone; SD, standard deviation; SHBG, sex hormone-binding globulin.

* Corresponding author.
E-mail address: matias.castro@hospitalitaliano.org.ar (H.M. Castro).

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Conclusions: The prevalence of hypogonadism was high and greater in COPD vs non-COPD men. This study suggests that COPD patients should be screened for hypogonadism.
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PALABRAS CLAVE
Enfermedad pulmonar obstructiva cronica;
Comorbilidades;
Hipogonadismo;
Hormonas;
Testosterona

Prevalencia de hipogonadismo en hombres con y sin enfermedad pulmonar obstructiva cronica: estudio de corte transversal

Resumen
Introducción: El hipogonadismo es frecuente en pacientes con enfermedad pulmonar obstructiva crónica (EPOC). Sin embargo, la prevalencia de hipogonadismo varía entre estudios. El objetivo del estudio fue determinar y comparar la prevalencia de hipogonadismo en hombres con y sin EPOC.
Métodos: Se realizó un estudio de corte transversal que incluyó a 134 pacientes con EPOC estable y 70 hombres sin EPOC pareados por edad. Se definió el hipogonadismo por la presencia de síntomas según el cuestionario de Androgen Deficiency in Aging Males y una deficiencia de testosterona total (<300 ng/dL).
Resultados: Los pacientes tenían una edad media de 68 años (DE 6), un índice de masa corporal de 28 kg/m^2 (DE 6) y el 17% eran fumadores. La prevalencia de hipogonadismo fue del 41,8% en hombres con EPOC (N = 56, IC 95% 33-51) y del 10,0% en hombres sin EPOC (N = 7, IC 95% 4-20), con una razón de prevalencia de 4,2 (IC 95% 2,0-8,7, p < 0,001). La prevalencia de concentraciones bajas de testosterona total (< 300 ng/dL) fue significativamente mayor en los pacientes con EPOC que en el grupo de control (47,0% frente a 15,7%, p = <0,001). En el grupo de pacientes con EPOC, el 89,3% presento un hipogonadismo hipogonadotropo y el 10.7% un hipogonadismo hipergonadotropo. La prevalencia de hipogonadismo fue mayor en pacientes con EPOC grave que en los no graves (55,8% versus 35,2%, p = 0,024).
Conclusiones: La prevalencia de hipogonadismo fue alta y mayor en hombres con EPOC que en hombres sin EPOC. Este estudio sugiere que los pacientes con EPOC deben ser evaluados para detectar hipogonadismo.
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Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide,[1] with a global prevalence of 11.7%.[2] It often coexists with other diseases that have a negative impact on prognosis and health status.[3] One such condition is hypogonadism.[4] Hypogonadism has been associated with: muscle weakness, obesity, a decline in forced expiratory volume in the first second (FEV_1), anemia, infertility, gynecomastia, osteoporosis, sexual dysfunction, decreased libido, and depression.[5]

Former studies have reported varying prevalence rates of hypogonadism in men with COPD, from 22 up to 69%.[6,7] There is controversy regarding whether the prevalence of hypogonadism is higher in individuals with COPD vs the general population.[7–10] The prevalence of hypogonadism in COPD patients in Latin America is unknown.

The main objective of this study was to determine the prevalence of hypogonadism in men with COPD and compare it with that of men without COPD.

Methods

We conducted an analytical cross-sectional study to compare the prevalence of hypogonadism in adult men with COPD to that of non-COPD men in an Argentine tertiary referral center from January 2018 through January 2019.

A consecutive sampling of COPD and non-COPD patients was obtained. A total of 193 men with COPD who attended the Pulmonology Service at Hospital Italiano de Buenos Aires for outpatient evaluation were assessed for eligibility. The study participants were included if they were men older than 40 years with a diagnosis of COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, and in a clinically stable condition (without exacerbation over the past 4 weeks). Exacerbation was defined as an acute worsening of respiratory symptoms (increased dyspnea, cough or sputum production). Individuals were excluded due to treatment with androgens, antiandrogens, ketoconazole, gonadotropin-releasing factor analogues, cimetidine, phenytoin, opioids, carbamazepine,

chronic administration of systemic glucocorticoids, comorbidities that may cause a decrease in testosterone levels, acute disease or inability to perform the spirometry. After applying these criteria, 59 subjects were excluded from the study and 134 COPD patients were eventually enrolled.

In addition, a group of non-COPD men from the outpatient endocrinology service at the same hospital were enrolled. Subjects with a history of not smoking, COPD, respiratory symptoms, and without other pulmonary diseases were included. Exclusion criteria were the same ones as those for the COPD group. Seventy age-matched non-COPD men were eventually enrolled.

Data collected for each subject included clinical characteristics, demographics and comorbidities, the administration of the Clinical Androgen Deficiency in Aging Males (ADAM) questionnaire, and the body mass index (BMI). All COPD patients underwent post-bronchodilator spirometry.

Hormone studies

Blood samples were drawn from 8:00 through 11:00 AM, following an 8-h fasting period. Total testosterone and sex hormone-binding globulin (SHBG) levels were measured by electrochemiluminescence (Cobas 801, Roche). Luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels were measured by chemiluminescence (Alinity, Abbott). Free testosterone was estimated by the Vermeulen method.[11] Inter- and intra-assay coefficients of variation were as follows: total testosterone, $\leq$6% and 2.5%; SHBG, $\leq$4% and 1.9%; LH, 4.7% and 4.3%; FSH, 2.7 and 2.2%. Reference values were LH (2–12 mIU/mL); FSH (1–12 mIU/mL); SHBG (13–71 nmol/L); total testosterone (249.0–836.0 ng/dL); free testosterone (68.5–137.3 pg/mL). Decreased total and free testosterone levels were defined as values <300 ng/dL and <65 pg/mL, respectively. The presence of hyperprolactinemia and thyroid disease was ruled out.

Definition of hypogonadism

Hypogonadism was defined as the presence of symptoms along with biochemical evidence of testosterone deficiency.[12–14] The presence of symptoms was assessed using the ADAM questionnaire,[15] which is a self-administered 10-item questionnaire that is answered with yes or no (see supplementary material 1). The ADAM questionnaire was considered positive if the subject answered ''yes'' to questions 1 and 7 or, at least, to 3 other questions. The cut-off point used for total testosterone was 300 ng/dL based on recommendations given by the American Urological Association and the 5th percentile of the reference value for healthy, non-obese young men according to the Endocrine Society.[13,16]

The study was conducted following the statement of ethical principles for medical research involving human subjects outlined in the Declaration of Helsinki and the Good Clinical Practice guidelines. Approval from Hospital Italiano de Buenos Aires Research Ethics Committee was obtained (No. 2413). All subjects signed a written informed consent form prior to being included in the study.

Severity of COPD

COPD severity was assessed through the degree of obstruction measured by FEV_1 (%) in post-bronchodilator spirometry. COPD patients with FEV_1 <50% were categorized as severe and those with FEV_1 $\geq$50% as non-severe.

Sample size

Sample size was estimated based on the previously reported prevalence rate of hypogonadism of 26% in COPD (p1), and 10% in controls (p2).[17] Taking into account a power of 80% ($1-\beta$), a level of significance of 0.05 (α), and a COPD/non-COPD ratio of 2, the number of patients to be recruited was estimated at 140 for COPD patients and 70 for non-COPD patients.[18]

Statistical analysis

Continuous variables were expressed as mean and standard deviation or as median and interquartile range depending on the observed distribution. Categorical variables were expressed as proportions. The estimated prevalence of hypogonadism was reported as absolute numbers for each frequency and their percentage with the corresponding 95% confidence interval (95%CI). The inter-group prevalence of hypogonadism was compared using the chi-square test. The inter-group prevalence ratio of hypogonadism and its 95% confidence interval were calculated. Inter-group differences in continuous variables were assessed using the *t*-test or the Wilcoxon test and the categorical variables were assessed using the chi-square test or Fisher's exact test, as appropriate. A multivariate logistic regression analysis was performed to evaluate the association between COPD and hypogonadism adjusting for potential confounders such as age, BMI, and type 2 diabetes mellitus. Relationships between BMI and total testosterone were studied using Spearman correlations coefficient (r_s). Statistical significance was set at a *p*-value <0.05. All statistical analyses were performed using STATA software (Version 13).

Results

A total of 134 men with stable COPD and 70 non-COPD men were included in the study. Fig. 1 shows the patient enrollment flow chart.

Patients had a mean age of 68.3 years (SD, 6.6), a mean BMI of 28 kg/m^2 (SD, 6.6), and 17% were current smokers. No statistically significant differences were found in age, BMI, or the presence of type 2 diabetes mellitus between COPD and non-COPD patients. Table 1 summarizes the clinical characteristics and testosterone levels of the enrolled patients.

The prevalence of hypogonadism was higher in COPD than in non-COPD patients (Fig. 2), with a prevalence ratio of 4.20 (95%CI, 2.0–8.7; $p < 0.001$). COPD patients exhibited lower levels of total testosterone (Fig. 3) and free testosterone (Table 1) vs non-COPD patients. The prevalence of low total testosterone concentrations was significantly higher in COPD

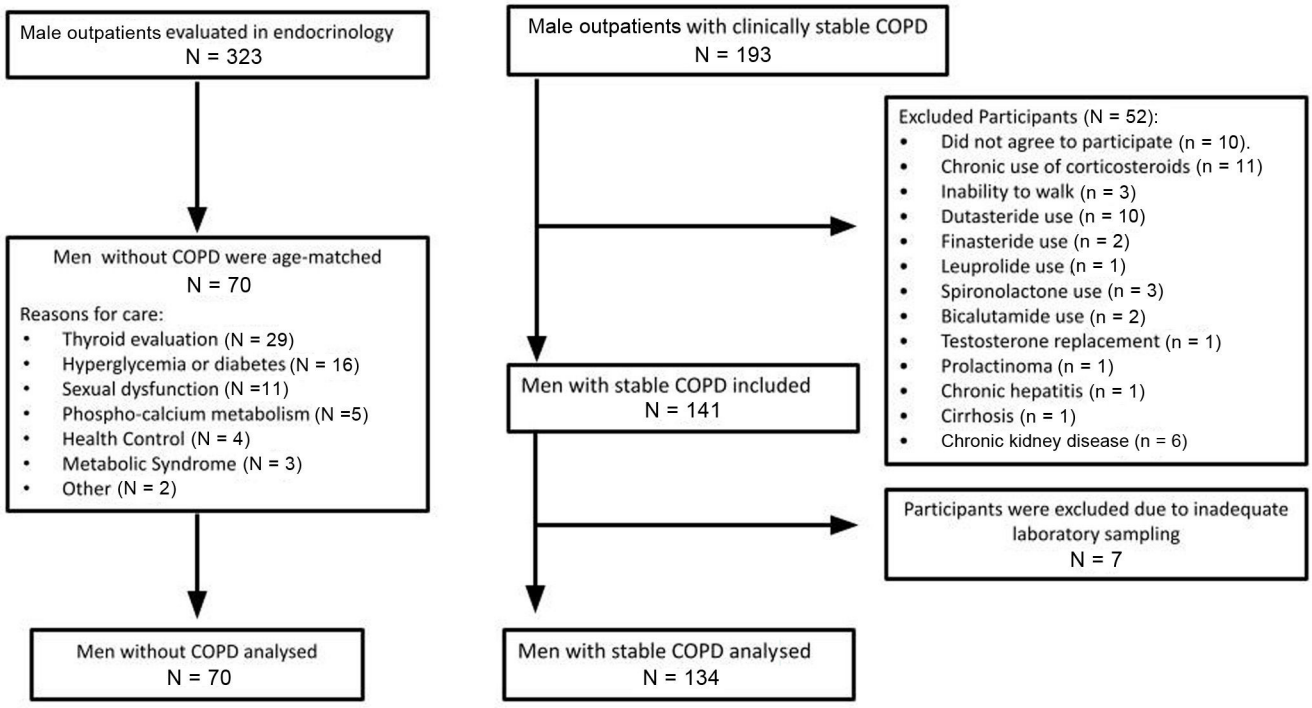

Figure 1 Flow chart of patients enrolled with and without COPD.

Table 1 Clinical characteristics and testosterone levels in men with and without stable chronic obstructive pulmonary disease.

Variables	COPD ($N = 134$)	Non-COPD ($N = 70$)	p
Age in years, mean (SD)	68.2 (7.5)	68.3 (4.5)	0.887
BMI in kg/m^2, mean (SD)	27.8 (4.5)	28.5 (4.1)	0.227
Smoking, n (%)			
Never	0 (0)	70 (100)	<0.001*
Former	99 (73.8)	0 (0)	
Current	35 (26.2)	0 (0)	
Obesity, n (%)	33 (24.6)	20 (28.6)	0.542
Type 2 diabetes mellitus, n (%)	17 (12.7)	15 (21.4)	0.103
SHBG nmol/L, median (IQR)	41.9 (30.5–57.6)	46.6 (36.2–58.6)	0.269
Free testosterone, median pg/mL (IQR)	51 (40.4–63.3)	78.1 (60.9–84.8)	<0.001*
Total testosterone ng/dL, median (IQR)	310 (230–380)	430 (350–500)	<0.001*
Total testosterone <300 ng/dL, n (%)	63 (47)	11 (15.7)	<0.001*

COPD, chronic obstructive pulmonary disease; SD, standard deviation; BMI, body mass index; IQR, interquartile range; SHBG, sex hormone-binding globulin.
* $p < 0.05$.

vs non-COPD patients (47.0% vs 15.7%; $p = <0.001$). No inter-group differences in SHBG values were reported (Table 1). A total of 70.2% ($N = 94/134$) of COPD patients had low free testosterone concentrations.

A total of 32.1% ($N = 43$) of patients had severe COPD (FEV_1 <50%). The prevalence of hypogonadism was higher in severe COPD patients vs non-severe COPD patients (55.8% vs 35.2%; $p = 0.024$).

In the COPD group, 50 of 56 hypogonadal patients (89.3%) exhibited normal or low LH values ($\leq$12 U/L), suggesting hypogonadotropic hypogonadism. The remaining 6 patients (10.7%) had appropriate elevations of LH levels (>12 U/L), suggesting testicular dysfunction with hypergonadotropic hypogonadism. Regarding FSH, 36 patients (64.3%) had normal or low levels (FSH $\leq$20 U/L) and 20 (35.7%) had high levels (FSH >20 U/L), with predominance of secondary hypogonadism. A total of 85.7% ($N = 6/7$) of the patients from the non-COPD hypogonadal group had hypogonadotropic hypogonadism while 14.3%, hypergonadotropic hypogonadism.

An association was seen between COPD and hypogonadism. The odds of hypogonadism were significantly

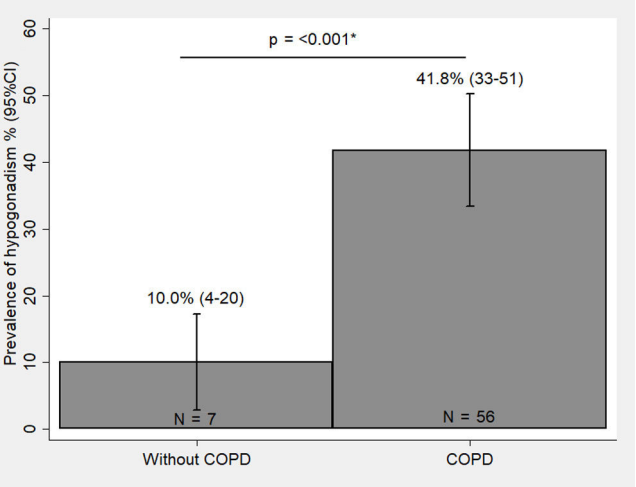

Figure 2 Prevalence of hypogonadism in men with and without COPD. The prevalence of hypogonadism was greater in COPD vs non-COPD men. Error bars represent the 95% confidence interval. COPD, chronic obstructive pulmonary disease; *chi-square test.

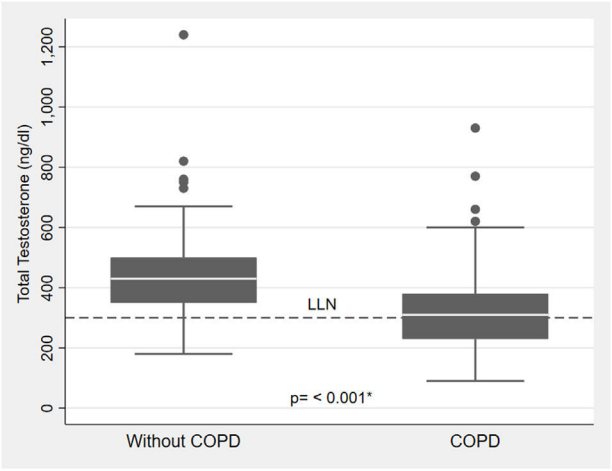

Figure 3 Total testosterone levels in men with COPD and without COPD. The median total testosterone levels were lower in COPD patients. The middle line marks the median; boxes indicate the interquartile range; whiskers represent the upper and lower quartiles and dots represent outliers. Horizontal dashed lines represent the lower limit of normal (LLN). COPD, chronic obstructive pulmonary disease; *Wilcoxon–Mann–Whitney test.

higher in COPD vs non-COPD patients, regardless of age, BMI, and the presence of type 2 diabetes mellitus (Table 2).

In the COPD group, BMI was inversely related to total testosterone levels ($r_s = -0.36$; $p = <0.001$). No significant differences were found between median total testosterone levels stratified by current inhaled corticosteroid use, current smoking, and type 2 diabetes mellitus (see supplementary material 2–4).

Table 2 Multivariate analysis for the association between COPD and hypogonadism in men.

Variable	Multivariate analysis OR adjusted (95%CI)	*p*-Value
Age, years	0.99 (0.95–1.03)	0.783
Body mass index, kg/m^2	1.04 (0.97–1.12)	0.235
Type 2 diabetes mellitus	1.52 (0.62–3.74)	0.359
COPD	7.06 (2.97–16.8)	<0.001

OR, odds ratio; 95%CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease.

Discussion

This study showed four main findings. Firstly, the prevalence of hypogonadism in COPD men was high and greater than in non-COPD men. Secondly, testosterone levels were lower in COPD vs non-COPD men. Thirdly, the prevalence of hypogonadism was higher in severe COPD. Lastly, in both groups, most hypogonadal patients had hypogonadotropic hypogonadism.

According to international guidelines, diagnosis of hypogonadism is defined by the presence of symptoms along with low testosterone levels.[19] Considering the presence of symptoms and low total testosterone levels (<300 ng/dL), we found a prevalence of hypogonadism of 41.8% in COPD men vs 10.0% in non-COPD men.

The previously reported prevalence of hypogonadism in COPD was 22% up to 69%.[4] The wide range of prevalence reported for hypogonadism may be attributed to differences in sample characteristics such as age, inclusion/exclusion criteria, associated comorbidities, use of chronic systemic corticosteroids or opioids, and sample size, as well as the diagnostic criteria used for defining hypogonadism (free or total testosterone, units, cut-off point, and measurement method used). These differences impair the comparison between studies. Only one study considered the presence of symptoms; the others defined hypogonadism based on low levels of total or free testosterone. Considering the presence of symptoms, a study[17] reported a prevalence of hypogonadism associated with COPD of 25.5%. The higher prevalence stated by our study may be partly explained by the larger number of patients with severe disease (56% vs 33%).

In COPD patients, the range of total and free testosterone deficiency has been reported to be around 22% up to 58%[9,17,20-22] and 22% up to 69%,[6,7,17,23,24] respectively. In this study, the prevalence of total and free testosterone deficiency in COPD was 47% and 70%, respectively, which is consistent with previously reported ranges. As the testosterone threshold that triggers symptoms of hypogonadism varies significantly between individuals,[25] the use of this measurement in isolation has limitations and may overestimate the prevalence of hypogonadism.

The prevalence of hypogonadism was higher in severe COPD vs non-severe COPD patients. These findings are consistent with the results of former studies.[17,26]

The prevalence of hypogonadism in non-COPD men (10%) in this study was similar to that reported by the Massachusetts male aging study. This study used a similar definition and found a prevalence of hypogonadism of 9.4% in adult men aged 60–70 years.[27] This similarity suggests that the sample of non-COPD patients in our study may be representative of the general population.

The prevalence of hypogonadism was 4-fold higher in COPD vs non-COPD men. Similar results have been found in all studies that use control groups. In agreement with our findings, several publications[9,17,20,23] have reported a higher prevalence of hypogonadism in COPD patients vs their respective control groups, with differences ranging from 10% up to 30%. Also, having COPD was associated with a 7-fold increase in the likelihood of developing hypogonadism vs patients without COPD, regardless of age, BMI, and type 2 diabetes mellitus. In line with this finding, a study reported that in COPD men, the OR of having hypogonadism was 1.4-fold higher vs non-COPD men[28] and another study found that COPD increases the OR for hypogonadism 24-fold, regardless of age and comorbidities.[29]

This study found that 89% of hypogonadal COPD patients had hypogonadotropic hypogonadism, which is consistent with the findings of other studies,[7,23] which reported hypogonadotropic hypogonadism in 76% and 73% of cases of hypogonadal COPD patients. These findings might be attributed to an impairment of the hypothalamic–pituitary–gonadal axis due to hypoxemia or chronic inflammation or dysfunction of Leydig cells in the testes or a combination of all these factors.[7,8]

Based on former studies, BMI presented an inverse relationship with testosterone levels.[8,22]

Limitations

Our study has some limitations that need to be acknowledged. Firstly, the use of a single measurement for testosterone levels may lead to imprecise data due to significant intraindividual variation.[30] However, we should mention that all former studies have also used a similar approach. Secondly, the study was conducted at a single tertiary health center, which may restrict the generalizability of our findings and result in a selection bias for severe COPD cases and these results may not be representative of the prevalence of hypogonadism among COPD patients in Argentina. Thirdly, there is potential information (classification) bias in non-COPD patients since no spirometry was ever performed to rule out COPD. However, this bias is unlikely in our sample because all non-COPD patients were non-smokers and the prevalence of COPD reported in non-smokers in Argentina is low (18%).[31] Fourthly, the study reliance on non-smoking status as the sole criterion for defining non-COPD men might introduce bias, as smoking could also impact the sexual function. Although the relationship between smoking and testosterone levels has been inconsistent in the literature, most observational studies suggest that smoking in men increases total testosterone.[32] In addition, only 26% of COPD patients were former smokers.

Strengths

Despite our limitations, this study has several strengths. Firstly, the study included a well-defined control group of non-COPD men. Secondly, the diagnosis of hypogonadism considered the presence of symptoms based on a validated questionnaire and adhered to a globally accepted threshold of total testosterone deficiency, as recommended by international guidelines.[19] Lastly, this is the second largest sample size study to estimate the prevalence of hypogonadism in COPD.

Implications and future research

Hypogonadism has an impact on the patient's quality of life; it is associated with decreased libido, sexual dysfunction, osteoporosis and fracture risk, anemia, and infertility.[13] Given the high prevalence of hypogonadism in COPD patients, these patients should be screened for symptoms of hypogonadism that may prompt a biochemical diagnosis to determine which patients would benefit from testosterone replacement therapy. Randomized, controlled clinical trials are needed to evaluate the efficacy of testosterone replacement therapy on quality of life and exercise tolerance in COPD patients.

Conclusion

In conclusion, this study found four major results: (1) the prevalence of hypogonadism in COPD was high and higher vs non-COPD men, (2) testosterone levels were lower in COPD vs non-COPD men, (3) the prevalence of hypogonadism was higher in severe COPD vs non-severe COPD men, and (4) in most cases, hypogonadotropic hypogonadism was found. The study also found that the prevalence of hypogonadism was 4-fold higher in COPD vs non-COPD men. Based on the findings of this study, COPD patients should be assessed for hypogonadism.

Funding

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.endinu.2024.05.010.

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