Journal of Current Biomedical Reports
Volume 3, Number 3, 2022
jcbior.com
eISSN: 2717-1906

Original research

The association between subclinical hypothyroidism and exacerbation in patients with chronic obstructive pulmonary disease

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Abstract

This study aimed to investigate the association between subclinical hypothyroidism and exacerbation in patients with chronic obstructive pulmonary disease (COPD). This descriptive-analytical study was performed on patients with COPD that were diagnosed by spirometry and GOLD guides. A modified medical research council (mMRC) questionnaire was also used for grading dyspnea. The severity of the disease was determined according to the GOLD criteria. Patients were divided into mild, moderate, severe, and very severe COPD. Then, the patients were included in high-risk (C and D) and low-risk (A and B) groups. Thyroid-stimulating hormone (TSH), free thyroxine, triiodothyronine (T3), and T3 resin uptake tests were assessed. Out of 119 patients with COPD, about 74.8% were males and 25.2% were females. Overall, 50.4% of participants were in an exacerbation state and 49.6% were stable. A significant association was reported between the number and years of cigarette smoking and the exacerbation of COPD ($P<0.05$). There was a significant association between severity in exacerbation and stable groups ($P<0.05$). The frequency of dyspnea grade with high mMRC scores in the exacerbation group was higher than in the stable group. The mean difference in FEV1, FVC, FEV1/FVC, and T3 variables was significant between the two studied groups. There was a significant difference between the variables of "one-year hospitalization", "one-year exacerbation" and "duration of illness" among the two groups of stable and exacerbation ($P<0.05$). It's suggested that the mean level of T3 could be used in the future to predict disease exacerbation in COPD.

Keywords: COPD, Thyroid-stimulating hormone, Airflow obstructions, Chronic, Exacerbation

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the main causes of morbidity and mortality in the world which led to a decline in the quality of life and premature death of its complications [1, 2]. COPD is defined as chronic bronchitis, emphysema, or progressive obstruction of the airway. Patients with COPD are usually hypoxic and hypercapnic. In addition, the level of systemic inflammatory markers in patients with COPD increases [3-5]. Despite the frequent recurrence and consequences of exacerbation of COPD, the underlying pathologic mechanism has

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Received: February, 16, 2022
Accepted: May, 03, 2022

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remained unknown. However, there is compelling evidence that COPD cannot be a disease confined to the lung [6]. Today, patients with COPD are diagnosed with chronic inflammation of the lung and systemic blood circulation [1]. Endocrine organs are involved in patients with severe COPD who develop hypoxemia and hypercapnia [7]. Thyroid disorders are common in chronic diseases such as COPD [1]. The most common thyroid diseases are hypothyroidism and hyperthyroidism. Based on the level of thyroid-stimulating hormone (TSH) in subclinical hypothyroidism (TSH levels between 4.5 and 10 with normal FT4 level), thyroid disorders were categorized into hypothyroidism and hyperthyroidism [8, 9]. Studies have shown that clinical symptoms of dyspnea respiration, airway obstruction, sleep apnea, reduced response to chemical stimuli, hypercapnia, and respiratory failure can play an effective role in hypothyroidism [10-12]. In addition, expiratory/inspiratory pressure is significantly reduced in hypothyroidism [7, 9, 13]. Moreover, diaphragmatic dysfunction in hypothyroidism [14] and an inverse association have been reported between TSH and inspiratory-expiratory muscle length in patients with hypothyroidism [15]. Decreased thyroid function in COPD patients may occur as subclinical, overt hypothyroidism overt, and non-thyroid disease syndrome (Euthyroid sick syndrome) [16, 17]. Hypothyroidism in patients with COPD can increase respiratory exercise and the risk of sleep respiratory disorders. In addition, hypothyroidism can reduce respiratory muscle function and decrease the activity capacity of patients with COPD [7]. Hyperthyroidism may also impair respiratory muscle function and activity in patients with COPD. Both maximal inspiratory and expiratory pressure (MIP and MEP) would decrease with the increase of hyperthyroidism [7, 18]. Functional disorders may be due to reduced respiratory muscle function, decreased lung capacity, and increased ventilation needs [19].

Thyroid gland dysfunction has many effects on the respiratory system including airway obstruction, respiratory muscle weakness, central apnea, sleep obstruction, alveolar hypoventilation, and pleural effusion. These clinical features have also contributed to the severity of exacerbation in COPD patients. Therefore, due to the importance of thyroid disorders in patients with COPD and the high prevalence of COPD disease, this study aimed to investigate the association between subclinical hypothyroidism and exacerbation in patients with chronic obstructive pulmonary disease (COPD) for better clinical management of patients with COPD.

2. Materials and Methods

2.1 Study design, categorization of patients, and sample size

This descriptive-analytical study was performed on patients with COPD, referred to Razi Hospital, Rasht, Iran, in 2019. Patients with COPD were entered into the study after obtaining informed consent. The diagnosis of COPD was based on spirometry in the Razi Hospital Respiratory test unit (JAEGER; Vyntus SPIRO PC spirometer) according to the GOLD guide. In this study, a modified medical research council (mMRC) questionnaire was used for grading dyspnea. The severity of the disease was determined according to GOLD criteria. Patients were divided into four groups according to spirometry criteria: mild, moderate, severe, and very severe obstruction. Diagnosis of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) was conducted based on the patient's clinical manifestations, such as aggravated dyspnea, cough, sputum production, overuse of maintenance therapy, or complementary therapies. In this study, patients were identified based on GOLD criteria including COPD exacerbation, dyspnea exacerbation, respiratory distress, hypoxemia (60> PaO2 mmHg), and hypercapnia (60<PaCO2 mmHg). Then, the patients were divided into high-risk (C and D) and low-risk (A and B) groups.

The venous blood samples of patients were collected and then, TSH, free Thyroxine (T4), triiodothyronine (T3), and T3 resin uptake (T3RU) tests were analyzed in Razi Hospital Laboratory in Rasht by ELISA (Pishtaz Teb, Iran). The normal values of thyroid hormones were TSH = 0.4-6 micIU / ml, T3 = 0.8-2.15 ng/ml, Free T4 = 0.7-1.8 pmol/dl, T3RU = 25%-35%. Patients who had TSH above 6 micIU / ml and had normal Free T4 were determined as subclinical hypothyroidism. The sample size was calculated as at least 30 patients (95% confidence and 85% test power) in each group based on the study of Osama et al. [20].

Patients with COPD were included in this study, who had an FEV1 / FVC ratio was less than 70%, and

also who had irreversible airway obstruction. Patients also were included in the study with mild, moderate, severe, and very severe COPD, as well as exacerbation COPD. In the current study, patients were not included in the study who needed admission to the intensive care unit (ICU). Patients were excluded from the study who had received systemic corticosteroids, iodine, amiodarone, or injectable contrast material over the past two months. Patients have also been excluded from the study who had a history of thyroid surgery, overt hypothyroidism or overt hyperthyroidism, a history of the treatment of thyroiditis, a history of neuromuscular and skeletal diseases, a history of anti-inflammatory drugs, a history of drugs, and patients with hypoxemia. Finally, 120 patients were assigned to the intervention and control groups. In the first group, 60 patients with COPD exacerbations and AECOPD were assigned. In the second group, 60 patients were assigned with stable COPD. Spirometry data related to the past year of patients with stable COPD were recorded in the information form.

2.2 Statistical analysis

The variables included age, sex, place of residence, occupation, history of comorbidities, physical examination, biochemical and thyroid function tests, and respiratory function tests (spirometry). Data were analyzed using SPSS version 21 software. The Kolmogorov-Smirnov test was used to test the normality of the data. For statistical analysis, the chi-square test was used to investigate the relationship between qualitative factors, and an independent t-test was used to compare the means between the two groups. Logistic regression analysis was performed to determine the variables associated with the severity of the disease. A significance level of tests was considered p-value ≤0.05.

3. Results

Out of 119 patients with COPD, about 89 (74.8%) participants were males and 30 (25.2%) participants were females. The patients were divided into two groups: exacerbation (60 participants (50.4%)) and stable (59 participants (49.6%)). According to Table 1, a significant association between the number and years of cigarette smoking and the exacerbation of COPD (P<0.05) was reported. In this regard, cigarettes smoking more than 20 packs per year might increase the risk of exacerbation. Also, a significant association was observed between the severity of COPD and exacerbation in the two groups (P <0.05). According to Table 2, more patients were eligible for subclinical hypothyroidism in the exacerbation group (P <0.05). The mean T3 was calculated to be 1.458 (ng/ml). T3 frequency (Table 2) showed that higher levels of T3 in COPD patients could be considered a risk factor for exacerbation (P <0.05). A higher frequency of dyspnea grade with high mMRC scores in the exacerbation group compared to the stable group was reported (Table 3). The mean of FEV1, FVC, FEV1/FVC, and T3 was significantly different between the two studied groups while for the other variables, no significant difference was reported among groups (P <0.05), (Table 4). There was a significant difference between the variables of "one-year hospitalization", "one-year exacerbation" and "duration of illness" between the two groups of Stable and Exacerbation (P <0.05), (Table 4).

4. Discussion

In patients with COPD, besides the lungs and airways, other organs of the body are also involved [21]. Systemic manifestations of COPD include dysfunction of the pituitary, thyroid, gonads, adrenal, and pancreas. Studies have shown that the severity of airway obstruction in COPD is associated with thyroid dysfunction [21, 22]. Many studies have shown that respiratory muscle strength decreases in patients with hypothyroidism, and this decrease may be related to neuropathy and myopathy [23]. In the El-Yazed et al. study [21], the mean of free T3, free T4, and TSH in patients with COPD was not significantly different from the control group. However, free T3 was higher in the COPD group than in the control group. Free T3 also increased with the increasing severity of COPD. Akter et al. conducted a study on patients with hypothyroidism [24]. Participants were divided into 3 groups A: healthy individuals in group B1 including untreated hypothyroid patients and group B2 including untreated hypothyroid patients. The mean percentages of both FEV1 and FVC were significantly lower in group B1 than in the other two groups. Akter's study showed that hypothyroid therapy could have a better effect on lung function.

Table 1. Frequency of cigarette smoking and severity of disease in patients with COPD

Groups	Variable	Exacerbation group No. (%)	Stable group No. (%)	Total No. (%)	P value
Cigarette smoking (Pack/years)	20<	21 (35)	37 (62.7)	58 (48.7)	0.015
	20≥	39 (65)	22 (37.3)	61 (51.3)	
Severity of disease	Mild	1 (1.7)	8 (13.6)	9 (7.6)	0.016
	Moderate	29 (48.3)	35 (59.3)	64 (53.8)	
	Severe	24 (40.0)	13 (22.0)	37 (31)	
	Very severe	6 (10.0)	3 (5.1)	9 (7.6)	

Table 2. Frequency of the levels of TSH and T3 in patients with COPD

Groups	Exacerbation group No. (%)	Stable group No. (%)	Total No. (%)	P value
TSH (micIU/ml)				
6≤	51 (85)	58 (98.3)	109 (91.6)	0.009
6>	9 (15)	1 (1.7)	10 (8.4)	
T3 (ng/ml)				
1.458≤	48 (80.0)	30 (50.8)	78 (65.5)	0.001
1.458>	12 (20.0)	29 (49.2)	41 (34.5)	

Table 3. Frequency of mMRC in patients with COPD

mMRC	Exacerbation group No. (%)	Stable group No. (%)	Total No. (%)	P value
1	0 (0)	10 (16.9)	10 (8.4)	0.001
2	16 (26.7)	21 (35.6)	37 (31.1)	
3	27 (45)	23 (39)	50 (42)	
4	17 (28.3)	5 (8.5)	22 (18.5)	

This study showed that hypothyroidism may decrease lung ventilation function and may be positively correlated with serum-free T4 levels and negatively correlated with serum TSH levels. In contrast, Laghi's study showed no association between T4-free, TSH, and pulmonary function tests [25]. According to our study, subclinical hypothyroidism was higher in the exacerbation group than in the stable group. There was also a significant difference in mean T3 between exacerbation and Stable groups. This study has the important message that by treating thyroid disorders, we may be able to decrease exacerbation and progression of COPD. Of course, the question arises as to which of the two, thyroid disorder or exacerbation of COPD, precedes the other? Given the role of thyroid hormones in the metabolism and physiology of the respiratory tract, a significant amount of these actions and reactions appear to be the primary outcome of thyroid disorders in COPD patients. This study showed a positive association between exacerbation of COPD and subclinical hypothyroidism.

In this study, healthy subjects were not included, in the control group, to more accurately examine the variables and indices. Another limitation of this study was the low sample size. Also, Thyroid and pulmonary function tests, as well as arterial blood gas (ABG) tests of patients, have not been studied.

Table 4. Demographical data and clinical characteristics of patients with COPD in different groups

Groups	**Exacerbation groups** (Mean±SD)	**Stable groups** (Mean±SD)	P value
Age	64.95±10.46	62.76±10.5±	0.259
Current smokers (Pack/years)	29.00±14.57	23.88±8.81	0.072
Cigarette smoking rates in a year (Pack/years)	21.58±10.91	20.64±5.49	0.753
FEV1(liter)	49.65±13.82	58.99±18.01	0.002
FVC (liter)	59.22±15.01	65.80±16.41	0.024
FEV1.FVC %	60.22±7.62	63.67±4.98	0.004
TSH (micIU/ml)	2.69±2.61	2.82±1.80	0.753
T3 (ng/ml)	1.23±0.40	1.51±0.47	0.001
T3 uptake %	30.24±2.2±	30.22±2.47	0.973
Free.T4 (pmol/dl)	1.25±0.32	1.26±0.33	0.778
Number of hospitalizations in the past year	1.40±1.15	0.97±1.27	0.001
Number of exacerbations in the past year	2.35±1.31	1.89±1.95	0.001
Duration of diseases	8.90±5.84	6.24±5.00	0.002

According to our results, the association between exacerbation of COPD and subclinical hypothyroidism was illustrated, and it seems likely that the mean T3 may be useful for physicians in the future to predict disease exacerbation.

Acknowledgments

We would like to thank all the hospital staff and specialists for their assistance with conforming and recording cases.

Authors' contributions

Concept and Study design: AJ, BV, AA, AT, BM. Methods, data collection, and experimental work: BV, ZR, STA, NF. Results analysis and conclusions: AJ, AA, AT, NF, BV. Manuscript preparation and editing: NF, BM. All authors read and approved the final version of the manuscript.

Conflict of interests

No potential conflict of interest was reported by the authors.

Ethical declarations

The study design was approved by the ethical committee at the Guilan University of Medical Sciences [IR.GUMS.REC.1397.263].

Financial support

Self-funding.

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