

Association Between Thyroid Function and Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Purpose: Chronic obstructive pulmonary disease (COPD) was the fourth leading cause of death in the world. Many studies have shown that COPD often exists with thyroid dysfunction; however, the relationship between thyroid function and COPD is often ignored in clinical. We retrospectively analyze the serum thyroid hormone levels in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and explore the association between thyroid function and AECOPD.

Methods: The study included patients hospitalized for AECOPD in our institution between January 2018 and September 2020. Patients with AECOPD were divided into moderate-to-severe and very severe groups based on lung function, and into normal and abnormal thyroid function groups based on thyroid hormone levels. Collected data and compared data between groups to identify risk factors for thyroid dysfunction in patients with AECOPD.

Results: The cohort included 97 in the moderate-to-severe group (72.39%) and 37 in the very severe group (27.61%). Compared with the very severe group, the moderate-to-severe group had higher triglyceride ($P=0.017$), high-density lipoprotein ($P<0.05$), partial pressure of carbon dioxide (PaCO_2 ; $P<0.05$), and serum thyroid-stimulating hormone (TSH; $P<0.001$). FEV_1 as a percentage of the predicted value ($\text{FEV}_1\%\text{pred}$) was positively correlated with TSH and FT_3 ($r=0.329$, $r=0.192$, respectively, both $P<0.05$). Duration of hospitalization was negatively correlated with TSH ($r=-0.256$, $P=0.003$). Among the 134 subjects, 98 (73.13%) had normal thyroid function and 36 (26.87%) had abnormal thyroid function. The two groups significantly differed regarding forced vital capacity (FVC), forced expiratory volume in 1 second, $\text{FEV}_1\%\text{pred}$, and albumin level. Logistic regression analysis showed that high FVC correlated with a low risk of thyroid dysfunction in AECOPD.

Conclusion: In patients with AECOPD, TSH is related to lung function and duration of hospitalization, and high FVC reduces the risk of thyroid dysfunction.

Keywords: AECOPD, thyroid hormone, retrospective cohort study, risk factor

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable chronic airway inflammatory disease. COPD was the fourth leading cause of death in the world in 2019 and is predicted to be the third leading cause of death in 2020.¹ In China, the estimated overall prevalence of COPD was 13.6% in 2014–2015,² and COPD was the fifth leading cause of death in 2016.³

COPD often exists with comorbidities that may significantly affect the disease course. Comorbidities not only affect symptom burden and health status but also affect the risk of hospitalization and mortality in patients with COPD.⁴ It is well

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known that the chronic inflammation of COPD is not just limited to the lungs, but spreads to other organs through the circulation.⁵ Comorbidities commonly recognized in patients with COPD include cardiovascular diseases, metabolic syndrome, osteoporosis, and anxiety. However, thyroid disease is also common in patients with COPD.⁶ A cross-sectional study from Spain showed that patients with COPD had a higher prevalence of thyroid disease (14.2%) than the expected standardized prevalence of chronic diseases (11.06%), and the prevalence of thyroid disease was higher in female than male patients (24.6% vs 10.9%).⁷ Acute exacerbation of COPD (AECOPD) and the exacerbation frequency have negative effects on quality of life and survival. We recalculated Gumus A's study data and found a decrease in triiodothyronine (T_3 ; 18.2%) and thyroid-stimulating hormone (TSH; 30.3%) in patients with exacerbation of COPD;⁸ furthermore, the exacerbation frequency was higher in patients with COPD with hypothyroidism than in those without hypothyroidism. The frequency of COPD exacerbation was positively correlated with TSH levels.^{9,10}

The abovementioned findings suggest that the relationship between thyroid function and COPD may be underestimated. Therefore, we reviewed the clinical data of patients with AECOPD who had been admitted to our hospital in the past 2 years, analyzed the relationship between thyroid function and severity of illness in patients with AECOPD, and explored the related risk factors.

Patients and Methods

Study Population

This was a retrospective cohort study. Data were collected from patients hospitalized for AECOPD in the Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Guangdong Medical University between January 2018 and September 2020. Collected data included demographics, smoking history, diagnosis, treatment, duration of hospitalization, thyroid hormone levels, serum biochemical indexes, lung function, and arterial blood gas findings.

For all included patients, COPD was clinically diagnosed and confirmed by lung function testing, and hospitalization was initiated because of AECOPD. The diagnosis of COPD and classification of severity were based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry guidelines. AECOPD was defined as an acute worsening of respiratory

symptoms that required additional therapy. Patients with AECOPD were divided in accordance with their lung function into a moderate-to-severe group (forced expiratory volume in 1 second as a percentage of the predicted value ($FEV_1\%$ pred) 30–79%) and a very severe group ($FEV_1\%$ pred <30%). The inclusion criteria were: (1) age ≥ 40 years; (2) moderate to very severe airflow limitation, post-bronchodilator FEV_1 /forced vital capacity (FVC) ratio <0.7 and $FEV_1\%$ pred <0.8; (3) detected serum thyroid hormone levels. The exclusion criteria were: (1) primary diagnosis of asthma; (2) severe bronchiectasis, pulmonary tuberculosis, or pulmonary fibrosis; (3) history of lung volume reduction surgery, pneumonectomy, or lung transplantation; (4) history of cancer; (5) history of thyroid disease, thyroid surgery, or administration of drugs containing iodine; (6) severe infection; (7) treatment administered before hospital admission.

Our study complied with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. As this was a retrospective study, informed consent of patient was not required by the Ethics Committee of Affiliated Hospital of Guangdong Medical University. The privacy of all participants was protected, we confirmed the data were anonymized and maintained with confidentiality.

Statistical Methods

SPSS statistical package (SPSS 22.0, IBM, USA) was used for all data analyses. The distributions of continuous variables were examined using the Kolmogorov–Smirnov normality test. Continuous variables with normal distribution were presented as mean \pm standard deviation, while continuous variables with non-normal distribution were presented as median and interquartile range (IQR). The chi-squared test was used to compare categorical variables between the moderate-to-severe group and the very severe group. Correlations among variables were analyzed using Spearman correlation test. Binary regression analyses were performed to evaluate the potential independent association between thyroid function and each of the assessed parameters. $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 134 patients with AECOPD were included, including 97 (72.39%) in the moderate-to-severe group and 37 (27.61%) in the very severe group. The two groups

did not differ regarding age, sex, BMI classification, smoking status and course of disease. Blood gas analysis showed a lower PaCO₂ in the moderate-to-severe group than the very severe group (43.30 mmHg vs 47.80 mmHg; $P<0.001$), but no intergroup differences in pH and PaO₂. The serum triglyceride level was higher in the moderate-to-severe group than in the very severe group (0.91 mmol/L vs 0.80 mmol/L; $P=0.017$), while the high-density lipoprotein level was lower in the very severe group than in the moderate-to-severe group (1.37 mmol/L vs 1.54 mmol/L, $P=0.025$). The other assessed biochemical indexes (albumin, calcium ion, creatinine, urea, uric acid, total cholesterol, and low-density lipoprotein) did not differ between the two groups. The TSH level significantly differed between the two groups ($P=0.001$), but the FT₃ and FT₄ did not (Table 1, [Supplemental Table 1](#))

Correlations Between FEV₁%pred, PaCO₂, PaO₂, Duration of Hospitalization, and Thyroid Hormone Levels

There were no correlations between the thyroid hormone levels and either PaCO₂ or PaO₂. However, TSH and FT₃ were positively correlated with FEV₁%pred ($r=0.329$ and $r=0.192$, respectively, both $P<0.05$). The duration of hospitalization was negatively correlated with TSH ($r=-0.256$, $P=0.003$), but was not correlated with FT₃ and FT₄ (Table 2).

Thyroid Hormone Levels in Patients with AECOPD

We separated all patients into two groups in accordance with the serum thyroid hormone levels (normal ranges of serum FT₃, FT₄, and TSH: 2.3–6.8 pmol/L, 10–23.5 pmol/L, and 0.34–4.0 mIU/L, respectively); the normal thyroid hormone group (normal group) comprised 98 patients (73.13%) and the abnormal thyroid hormone group (abnormal group) comprised 36 (26.87%). The two groups did not differ regarding age, sex, BMI classification, smoking status. The FVC, FEV₁, and FEV₁%pred were higher in the normal group than the abnormal group (1.82 vs 1.38, 0.91 vs 0.7, and 42.72% vs 35.39%, respectively, all $P<0.05$). Blood gas analysis revealed that pH, PaO₂, and PaCO₂ did not differ between the two groups. The serum albumin level was higher in the normal group than the abnormal group (39.15 g/L vs 37.47 g/L, $P=0.033$), but the other assessed biochemical indexes did not differ between the two groups (Table 3, [Supplemental Table 2](#)).

Risk Factors for AECOPD Complicated with Abnormal Thyroid Function

Table 4 shows that smoking history, FVC, FEV₁, and FEV₁%pred significantly differed between the normal and abnormal groups. We analyzed these data using binary regression analyses to identify the risk factors for abnormal thyroid function in patients with AECOPD. The FVC tended to be a protective factor to reduce the prevalence of abnormal thyroid function in patients with AECOPD (OR 0.114, 95% CI 0.015–0.887), while the other assessed variables showed no association with thyroid function.

Discussion

COPD is a respiratory disease that is prevalent worldwide and has chronic airway inflammation as is its major characteristic. In addition to airway inflammation, patients with COPD have inflammation in other body systems. The GOLD guidelines state that COPD is often complicated with many diseases,¹¹ but thyroid dysfunction may be an underestimated complication of COPD due to insufficient clinical data. As we know, COPD patients often had a smoke history. Both cigarette smoke and chronic inflammatory in COPD itself can impair the thyroid gland, and lead to abnormal thyroid hormone production.¹² Karadag et al demonstrated that the prevalence of non-thyroidal illness syndrome (abnormal thyroid hormone levels not due to thyroid disease) was 14–20% in patients with stable COPD, and 70% in patients with AECOPD.¹³ Of the 134 patients with AECOPD in the present study, approximately 26.87% had abnormal thyroid hormone levels. Due to the difference of AECOPD inclusion criteria between us, our data shown the prevalence of AECOPD with abnormal thyroid function was lower than in the study by Karadag et al.¹³ But our findings still suggest that thyroid dysfunction is common in patients with AECOPD.

Thyroid hormones play an important role in the regulation of metabolism by enhancing mitochondrial oxidation and augmenting the metabolic rate.¹⁴ The effect of thyroid hormones on the metabolic rate is probably responsible for the relationship between thyroid hormone levels and respiratory drive.¹⁵ Both hypothyroidism and hyperthyroidism can impair respiratory muscle function, respiratory mechanics, and exercise capacity in patients with COPD.¹⁶ Lung function (especially FEV₁%pred) is used as the basis for grading COPD and is closely related to the severity of AECOPD. Siafakas et al showed that in patients with hyperthyroidism, inspiratory and expiratory muscle

Table 1 Demographic and Clinical Characteristics of the Moderate-to-Severe Group Compared with the Very Severe Group

Characteristics	Moderate-to-Severe Group (n=97)	Very Severe Group (n=37)	P value
Demographic			
Age years-old, Mean (SD)	71.10(10.40)	67.60(8.60)	0.076
Male, Number (%)	68(70.1)	31(83.8)	0.127
Normal BMI kg/m ² , Median (IQR) ^a	20.86 (3.2)	19.75 (2.99)	0.376
Low BMI kg/m ² , Median (IQR) ^b	17.10 (2.22)	16.27 (1.85)	0.108
High BMI kg/m ² , Median (IQR) ^c	26.91 (3.12)	27.05 (0)	0.710
Clinical			
Former smoker, Number (%)	25 (25.8)	14 (48.3)	0.203
Current smoker, Number (%)	25 (25.8)	15 (40.5)	0.138
Frequencies of AECOPD within one year \geq 2, Frequencies (%)	63 (64.9)	28 (75.7)	0.302
Course of disease-month, Median (IQR)	96(84)	120(60)	0.656
Lung function tests			
FVC-L, Median (IQR)	1.83(0.72)	1.47(0.41)	<0.001
FEV ₁ -L, Median (IQR)	0.98(0.43)	0.58(0.20)	<0.001
FEV ₁ %pred, Median (IQR)	47.65(11.99)	23.63(4.56)	<0.001
Blood gas analysis			
pH, Median (IQR)	7.42(0.04)	7.41(0.05)	0.603
PaO ₂ -mmHg, Median (IQR)	74.70(17.10)	72.60(20.35)	0.435
PaCO ₂ -mmHg, Median (IQR)	43.30(7.30)	47.80(8.30)	0.001
Biochemical indexes^d			
Albumin-g/L, Mean (SD)	38.74(4.14)	38.58(3.89)	0.836
Thyroid hormone levels			
FT ₃ -pmol/L, Median (IQR)	4.11(1.03)	3.91(1.64)	0.077
FT ₄ -pmol/L, Median (IQR)	15.42(5.86)	16.60(3.80)	0.502
TSH-mIU/L, Median (IQR)	1.05(1.16)	0.54(0.64)	0.001

Notes: ^aNormal BMI (18.5–24.9 kg/m²); ^bLow BMI (<18.5 kg/m²); ^cHigh BMI (\geq 24.9 kg/m²); ^dOthers of biochemical indexes see supplemental Table 1.

Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartile range (25th–75th percentile); AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEV₁%pred, FEV₁ as a percentage of the predicted value; FT₃, free triiodothyronine; FT₄, free tetraiodothyronine; TSH, thyroid-stimulating hormone; pH, pondus hydrogenii; PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen.

weakness (expressed as a reduction in the FEV₁, FVC, vital capacity, maximal expiratory pressure, and maximal inspiratory pressure) were positively correlated with the severity of hyperthyroidism;¹⁷ this was also supported by Terzano et al.¹⁸ Our results showed that the TSH level was higher in patients with moderate-to-severe AECOPD than

in those with very severe AECOPD. Furthermore, the FVC, FEV₁, and FEV₁%pred were higher in patients with AECOPD with normal thyroid hormone levels than in those with abnormal thyroid hormone levels. We further analyzed the association between thyroid hormone levels and lung function and found that the FEV₁%pred was

Table 2 Correlations Between FEV₁%pred, PaCO₂, PaO₂, Duration of Hospitalization, and Thyroid Hormone Levels

	FEV ₁ %pred		PaCO ₂		PaO ₂		Duration of Hospitalization	
	r	P	r	P	r	P	r	P
FT ₃	0.192	0.026	0.050	0.565	0.092	0.289	−0.137	0.115
FT ₄	−0.102	0.240	−0.031	0.720	0.137	0.114	0.052	0.550
TSH	0.329	<0.001	−0.108	0.214	0.004	0.959	−0.256	0.003

Abbreviations: PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen; FT₃, free triiodothyronine; FT₄, free tetraiodothyronine; TSH, thyroid-stimulating hormone; FEV₁%pred, forced expiratory volume in 1 second as a percentage of the predicted value.

Table 3 Clinical Data of Patients with AECOPD with Normal and Abnormal Thyroid Hormone Levels

Characteristics	Normal Thyroid Hormone Group (n=98)	Abnormal Thyroid Hormone Group (n=36)	P value
Demographic			
Age years-old, Mean (SD)	68.88(10.07)	70.86(10.13)	0.619
Male, Number (%)	76(77.6)	23(63.9)	0.124
Normal BMI kg/m ² , Median (IQR) ^a	20.96 (3.24)	20.54 (2.55)	0.692
Low BMI kg/m ² , Median (IQR) ^b	16.97 (1.69)	16.33 (2.79)	0.412
High BMI kg/m ² , Median (IQR) ^c	26.91 (3.06)	27.05 (4.91)	0.947
Clinical			
Former smoker, Number (%)	31 (31.6)	8 (22.2)	0.391
Current smoker, Number (%)	27 (27.6)	13 (36.1)	0.396
Lung function tests			
FVC-L, Median (IQR)	1.82(0.62)	1.38(0.46)	<0.001
FEV ₁ -L, Median (IQR)	0.91(0.48)	0.70(0.47)	<0.001
FEV ₁ %pred, Mean (SD)	42.72(15.01)	35.39(14.24)	0.030
Blood gas analysis			
pH, Median (IQR)	7.41(0.05)	7.42(0.05)	0.670
PaO ₂ -mmHg, Median (IQR)	74.15(20.30)	74.05(19.61)	0.690
PaCO ₂ -mmHg, Median (IQR)	44.50(9.26)	44.15(11.45)	0.458
Biochemical indexes^d			
Albumin-g/L, Mean (SD)	39.15(4.00)	37.47(4.01)	0.033

Notes: ^aNormal BMI (18.5–24.9 kg/m²); ^bLow BMI (<18.5 kg/m²); ^cHigh BMI (≥24.9 kg/m²); ^dOthers of biochemical indexes see supplemental Table 2.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; SD, standard deviation; BMI, body mass index; IQR, interquartile range (25th–75th percentile); FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEV₁%pred, FEV₁ as a percentage of the predicted value; pH, pondus hydrogenii; PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen.

positively correlated with the levels of TSH and FT₃. These results demonstrated that the severity of airway obstruction was associated with the levels of TSH and FT₃. These findings were consistent with Okutan O and Gao F's study.^{19,20} Ulasli et al found that TSH was the decisive factor in the frequency of AECOPD.⁹ In addition, Bacakoglu showed that low serum concentrations of FT₃ and FT₄ increased the incidence and mortality of invasive

mechanical ventilation in patients with respiratory failure.²¹ These findings suggest that thyroid hormone levels probably influence the prognosis of AECOPD. Therefore, we analyzed the relationship between TSH and the duration of hospitalization and found that these factors were negatively correlated. We speculate that this is related to the lower severity of AECOPD in patients with higher TSH which is positively correlated to FEV₁% pred. Furthermore, binary regression analysis revealed that the FVC was a protective factor to reduce the prevalence of thyroid dysfunction in patients with AECOPD.

The mechanism of thyroid dysfunction in COPD is not clear but may be related to hypoxemia and hypercapnia.²¹ Karadag et al found that TSH and FT₃ were lower in patients with COPD with severe hypoxemia than in patients with milder hypoxia.¹³ In contrast, some studies demonstrated that thyroid hormones were not correlated with pH, PaO₂, or PaCO₂.^{22,23} We also did not detect any relationship between TSH, FT₃, FT₄ and PaO₂ or PaCO₂. On the one hand, we speculate that this may be related to the fact that most of the

Table 4 Risk Factors for AECOPD Complicated with Abnormal Thyroid Function

Variables	OR	95% CI	P value
Smoking history	0.754	0.295~1.929	0.556
FVC	0.114	0.015~0.887	0.038
FEV ₁	1.930	0.042~87.975	0.736
FEV ₁ %pred	0.990	0.943~1.040	0.697
Albumin	0.929	0.831~1.038	0.194

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEV₁%pred, FEV₁ as a percentage of the predicted value.

patients included did not have respiratory failure; on the other hand, it may be related to the dynamic changes of hormones, PaCO₂, PaO₂ in the body, and dynamic observations may be better able to capture their correlations. Therefore, our team also plans to conduct prospective studies in order to provide more sufficient evidence for the relationship between thyroid hormones and AECOPD.

The results of the present study not only enhance the previous findings on the relationship between thyroid hormones and AECOPD but also add information that thyroid hormone levels influence the prognosis of AECOPD.

Limitation

As with all studies using retrospective information data, our study had some limitations. The clinical data that we could obtain from the medical record were limited. Therefore, we could not group subjects according to ABCD GOLD classification and perform more comprehensive comparisons between groups. Our findings were based on a single center and the sample size was limited, so the relationship between thyroid function and COPD maybe was underestimated or overestimated. Most stable COPD patients always inhaled hormones to control symptoms, we could not exclude it will affect the thyroid function. Although this study had some limitations, we hope these findings can raise clinical concerns about thyroid function in patients with COPD.

Conclusion

The clinical symptoms of thyroid dysfunction are often concealed by the symptoms of AECOPD, which leads to neglect and diagnostic difficulties. Our study shows that thyroid dysfunction is common in patients with AECOPD. Furthermore, serum TSH levels are positively correlated with the FEV₁%pred and negatively correlated with the duration of hospitalization. These findings suggest that the thyroid function should be monitored in patients with AECOPD because this is related to patient recovery.

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Disclosure

The authors of this study declare no conflicts of interest in this work.

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