CHANGES IN THYROID FUNCTION IN PATIENTS WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS CLINICAL SIGNIFICANCE

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ABSTRACT

Objective: To investigate the changes of thyroid function in patients with the acute exacerbation of chronic obstructive pulmonary disease (COPD) and its clinical significance.

Methods: In total, 239 patients with acute exacerbation of COPD (AECOPD) admitted to the Department of Respiratory Medicine, Jishuitan Hospital of Beijing from 2014 to 2017 were selected as the observation group, including 51 dead patients and 188 discharged patients who had improved. Fifty-six healthy people who received physical examination in the same period were selected as the control group. The levels of serum total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3), free thyroxine (FT4) and serum thyroid stimulating hormone (TSH) of 8AM, 4PM and 12MN were compared between the two groups after admission, and the oxygen and index and APACHE II score of the observation group were calculated.

Results: The levels of TT3, TT4 and FT3 in the improved group and the dead group were lower than those in the control group (P=0.000), but there was no significant difference between the improved group and the dead group (P>0.05); there was, however, a significant difference between the dead group and the improved group (P<0.000). The level of serum TSH in the observation group was lower than that in the control group (P<0.05), and the difference was significant at different time points (P<0.001). There was an interaction between groups and time at the level of serum TSH (P<0.001). The level of serum TSH in the observation group was lower than that in the control group (P<0.05). There was no significant difference in serum TSH level between the two groups (P>0.05), but there was a significant difference at different time points (P<0.001); however, there was no interaction between groups and time at serum TSH level (P>0.05). There was no significant difference in TSH levels between the non-respiratory failure, type I respiratory failure and type II respiratory failure groups (P>0.05); there was a significant difference at different time points (P<0.001), but no interaction between groups and time at the level of serum TSH (P>0.05). In the observation group, compared with the improvement group, the oxygenation index decreased significantly and APACHE II score increased significantly in the death group (P=0.000). TT3, oxygenation index and APACHE II score were independent predictors of death in AECOPD patients.

Conclusion: The hypothalamus-pituitary-thyroid axis may be impaired in patients with AECOPD. In severe AECOPD patients, hypoxia and thyroid hormone levels decreased more significantly.

Keywords: Chronic obstructive pulmonary disease, thyroid hormone, pituitary-thyroid axis, oxygenation index, APACHE II.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common and frequently-occurring disease that seriously endangers human health. It is expected to be the third leading cause of death in the world by 2020. COPD is a disease characterised by persistent respiratory symptoms and airflow limitation that can be prevented and treated. It is usually associated with airway and/or alveolar abnormalities caused by significant exposure to toxic particles or gases\(^1\).

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an important factor in the death of patients with chronic obstructive pulmonary disease. Chronic hypoxia and hypercapnia for a long time prompt COPD patients to develop multiple system complications. Studies have shown that COPD patients have abnormal thyroid hormone levels\(^2\-3\), manifested as hypothyroidism, subclinical hypothyroidism and non-thyroid disease syndrome (NTIS). NTIS is most common in 20% COPD patients in stable phase and 70% AECOPD patients\(^4\).
NTIS refers to the abnormality of thyroid function caused by non-thyroid diseases, surgery and fasting. It is caused by the abnormal uptake of thyroid hormone by the hypothalamus-pituitary-thyroid axis, thyroxin-binding plasma protein, tissue and/or abnormal metabolism of thyroid hormone. It is characterised by the decrease of triiodothyronine (T3) and normal or decreased levels of thyroxin (T4); usually, the level of serum thyrotropin (TSH) is normal. TSH is secreted periodically. Previous studies have shown that the fasting TSH levels of AECOPD patients were normal in the morning\(^2\)\(^-\)\(^3\). Therefore, this study retrospectively analysed the changes in thyroid hormone levels in AECOPD patients and further explored its clinical significance.

**Object and method**

**Research object**

The subjects included 239 patients with AECOPD in Department of Respiratory Medicine, Beijing Jishuitan Hospital from January 2014 to December 2017. Among them, 51 had died and 188 discharged patients had improved.

**Inclusion criteria:**

- Complying with the COPD diagnostic criteria (revised version in 2013) formulated by the Respiratory Disease Society of the Chinese Medical Association\(^5\), with a history of, symptoms consistent with and imaging manifestations of COPD. The forced expiratory volume/forced vital capacity (FEV1/FVC) <70% predicted value 1 second after inhalation of bronchodilator;
- AECOPD refers to acute exacerbation of respiratory symptoms in patients, the typical manifestations of which are increased dyspnoea and increased dyspnoea.
- Increased cough, increased sputum and/or purulent sputum show daily variations and lead to changes in medication. According to the results of blood gas analysis after admission, the patients were divided into three subgroups: 102 cases in the non-respiratory failure group, 51 cases in the type I respiratory failure group and 86 cases in the type II respiratory failure group.

**Exclusion criteria:**

- Patients with underlying thyroid diseases;
- Patients with bronchial asthma, pulmonary embolism, lung cancer, interstitial lung disease, acute respiratory distress syndrome and other respiratory diseases;
- Patients with heart disease, endocrine system disease, kidney disease and other serious complications;
- Patients who have used chemotherapeutic drugs, such as amiodarone hydrochloride, ethamiodarone, dopamine, etc. in the past three months, which may have affected thyroid secretion or generation;
- Those who need the long-term use of glucocorticoid due to immune system diseases;
- Pregnant women. At the same time, 56 healthy people in the Beijing Jishuitan Hospital were selected as the control group.

There were no cases of cardiovascular and cerebrovascular diseases, hypertension, diabetes, acute infections, and thrombotic, cancerous or haematological diseases, and they cooperated voluntarily. This study was approved by the Ethics Committee of Beijing Jishuitan Hospital and the subjects signed the informed consent.

**Research methods**

All AECOPD patients were given standard treatment after hospitalisation. The criteria for improvement and discharge were referred to the Chinese Expert Consensus on the Diagnosis and Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (2017 Update)\(^6\): Clinicians considered that patients could adapt to family medicine; patients could use long-acting bronchiectasis treatment, and inhaled short-acting beta-2 receptor agonists should be less than every 4 small. If the patient has not been in bed before, he should be able to walk indoors; the patients must be able to eat and sleep without the influence of dyspnoea; clinical stability of 12-24 hours; arterial blood gas analysis stability of 12-24 hours; patients (or family members) must fully understand the correct use of drugs in the stable period; and proper follow-up and family nursing plans must be followed.

Fasting venous blood was collected for thyroid function evaluation. Serum thyroid hormone levels were measured by the Roche E601 automatic electrochemiluminescence analyser at 8 a.m. after admission, including total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (TT3), FT3, and free thyroxine (FT4); reagents were provided by Roche.

TSH was assessed at 8 a.m. (8 AM), 4 p.m. (4 PM) and 12 p.m. (12 MN). Serum thyroid stimulating hormone (TSH) was detected by the Roche E601 automatic electrochemiluminescence analyser; the reagents were provided by Roche Company.

Evaluation of the oxygenation index and APACHE II score

All patients with AECOPD were sampled at
admission for blood gas analysis, and the oxygenation index was calculated according to the inhaled oxygen flow. Within 2 hours after admission, the APACHE II score was calculated according to the acute physiology and chronic health assessment II score system\(^7\). The APACHE II score was composed of acute physiology function score (APS), age and chronic health status score (CPS).

Statistical analysis was performed by using the SPSS 18.0 statistical software. The measurement data of normal distribution were expressed as \((\bar{x} \pm s)\). Single factor analysis of variance was used for comparison between groups. The LSD-t test was used for comparison between homogeneous groups and the Dunnett-t3 test was used for the analysis of variance between homogeneous groups; double factor repeated measurement analysis of variance was used for continuous measurement data, multiple factor logistic regression analysis was used for AECOPD mortality risk factors, and the \(\chi^2\) test was used for comparison between counting data groups. The difference was statistically significant with \(P<0.05\).

### Results

#### Comparison of general data between the two groups

A total of 239 patients were treated; of these, 188 patients were discharged and 51 died. There was no significant difference in gender and age between the two groups (\(P>0.05\)).

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Gender (male/female)</th>
<th>Age ((\bar{x} \pm s), years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>56</td>
<td>33/23</td>
<td>71.6±11.9</td>
</tr>
<tr>
<td>AECOPD group</td>
<td>239</td>
<td>165/74</td>
<td>77.8±9.0</td>
</tr>
<tr>
<td>(t) ((c^2))</td>
<td></td>
<td></td>
<td>1.668</td>
</tr>
<tr>
<td>(P)</td>
<td></td>
<td></td>
<td>0.197</td>
</tr>
</tbody>
</table>

Table. 1: Comparison of two groups of general information.

For thyroid function in AECOPD patients compared with the control group, the levels of TT\(_3\), TT\(_4\) and FT\(_3\) in the AECOPD improved group were significantly lower (\(P = 0.000\)), but there was no significant difference in FT\(_4\) level (\(P>0.05\)); the levels of TT\(_3\), TT\(_4\), FT\(_3\) and FT\(_4\) in the AECOPD death group were also significantly lower (\(P=0.000\)). Compared with the improvement group, the levels of TT\(_3\), TT\(_4\), FT\(_3\) and FT\(_4\) in the AECOPD death group decreased significantly (\(P=0.000\)) (see Table 2).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TT(_3)((\text{mmol/L}))</th>
<th>TT(_4)((\text{mmol/L}))</th>
<th>FT(_3)((\text{pmol/L}))</th>
<th>FT(_4)((\text{pmol/L}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>56</td>
<td>1.49±0.37</td>
<td>103.03±23.19</td>
<td>16.45±2.38</td>
<td>4.06±0.87</td>
</tr>
<tr>
<td>AECOPD improvement</td>
<td>188</td>
<td>1.05±0.34*</td>
<td>89.35±21.45*</td>
<td>16.17±2.91</td>
<td>3.06±0.81*</td>
</tr>
<tr>
<td>AECOPD death</td>
<td>51</td>
<td>0.72±0.19*</td>
<td>76.84±21.33*</td>
<td>14.45±2.85*</td>
<td>2.24±0.72*</td>
</tr>
<tr>
<td>(F)</td>
<td></td>
<td>74.78</td>
<td>19.42</td>
<td>8.73</td>
<td>68.67</td>
</tr>
<tr>
<td>(P)</td>
<td></td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table. 2: Comparison of serum thyroid hormone levels in the AECOPD improvement group, AECOPD death group and control group.

Note: Compared with the control group, *\(P=0.000\); compared with the AECOPD improvement group, \(P=0.000\). TT\(_3\)=total triiodothyronine, TT\(_4\)=total thyroxin, FT\(_3\)=free triiodothyronine, FT\(_4\)=free thyroxin.

#### Comparison of TSH Levels

Compared with the control group, the TSH level of AECOPD group showed significant differences (\(P<0.05\)); the TSH level of the AECOPD group was significantly different at various time points (\(P<0.001\)); the TSH level of the group showed significant differences over time (\(P<0.001\)). Among them, at 12 MN, the TSH level of the two groups was worse than that of the control group; the difference was statistically significant (\(P<0.05\)). There was no significant difference in TSH level in the AECOPD between the two groups (\(P>0.05\)); there was significant difference at different time points (\(P<0.001\)); there was no significant difference in TSH level between groups over time (\(P>0.05\), see Table 3).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TSH((\text{mIU/L}))</th>
<th>8AM</th>
<th>4PM</th>
<th>12MN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>56</td>
<td>1.67±0.89</td>
<td>1.60±0.64</td>
<td>3.23±0.88</td>
<td></td>
</tr>
<tr>
<td>AECOPD improvement</td>
<td>188</td>
<td>1.51±0.92</td>
<td>1.46±0.73</td>
<td>1.88±0.87*</td>
<td></td>
</tr>
<tr>
<td>AECOPD death</td>
<td>51</td>
<td>1.42±0.87</td>
<td>1.35±0.57</td>
<td>1.53±0.79*</td>
<td></td>
</tr>
<tr>
<td>(F)</td>
<td></td>
<td>F(<em>{group})=5.683, F(</em>{time})=173.831, F(_{mutual})=53.519</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(P)</td>
<td></td>
<td>(P_{group}=0.004, P_{time}=0.001, P_{mutual}=0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table. 3: Comparison of TSH levels in three groups.

Note: Compared with the control group, *\(P<0.001\); \(P<0.05\).

There was no significant difference in TSH level between the type I respiratory failure group, type II respiratory failure group, and non-respiratory failure group in AECOPD patients (\(P>0.05\)). There was a significant difference at different time points (\(P<0.001\)). There was no significant difference in TSH level between groups and times (\(P<0.001, P>0.05\), respectively; see Table 4).

### Table 4
Oxygenation index and APACHE II score of AECOPD patients were significantly lower in the AECOPD death group than in the improvement group, while the APACHE II score was significantly higher (P=0.000) (see Table 5).

Factors influencing the cause of AECOPD patient deaths were analysed by multivariate logistic regression. The results showed that TT3, oxygenation index and APACHE II score were independent predictors of AECOPD patient deaths (see Table 6).

Discussion

COPD is a common disability disease of the respiratory system. Due to long-term hypoxia, carbon dioxide retention and other factors, multiple system complications occur in the later stages. Severe hypoxaemia, systemic inflammation and glucocorticoid use in the acute exacerbation of COPD may cause decreases in thyroid hormone levels(8). Thyroid hormones play an important role in metabolism. Decreased thyroxin levels can lead to insufficient alveolar ventilation, decreased respiratory excitability and even respiratory failure(3), and can lead to muscle dysfunction(9), further reducing respiratory function.

The secretion of serum TSH in healthy adults has the characteristics of circadian rhythm and impulse secretion like other endocrine hormones(10). Serum TSH began to rise at night, peaked about 2 hours later, continued for about 4 hours (from 10 p.m. to 2 a.m.) and then began to decrease at 8 am the next day, reaching a low between 5 and 8:00 pm. It has been confirmed that the circadian rhythm of TSH is composed of a series of pulses. The average level of TSH at night is significantly higher than that at day, which is related to an increase in the number and amplitude of TSH pulses at night(11). The completeness of the circadian rhythm of TSH is of great significance for maintaining normal thyroid function(12). Studies have shown that the circadian rhythm of TSH is related to the circadian variation of thyroid iodine release and affects thyroid follicular function(11). The thyroid receives the main nutrient supply after the peak of TSH at night. If the circadian rhythm of TSH is disturbed, thyroid function will be affected even if the level of TSH is normal during the day.

This study showed that the levels of TT3, TT4, and FT3 in the AECOPD group were significantly lower than those in the control group, while the levels of TT3, TT4, FT3, and FT4 in the AECOPD group were lower still than those in the improved group, which is consistent with previous studies(13). This indicates that serum thyroid hormone levels can reflect the severity of AECOPD patients. Moreover, the TSH level of AECOPD patients was significantly lower than that of the control group at 12 MN, that is, the nocturnal secretion peak was absent, and there was no statistical difference between 8 a.m. and 4 p.m. There was no significant difference in TSH levels between the AECOPD death group and the improvement group. Considering the TSH night time secretion peak loss has a certain influence on the condition of AECOPD patients, the severity of AECOPD is also related to the interaction of more factors. The study also found that AECOPD patients in the type I respiratory failure group and type II respiratory failure group had lower TSH levels than those without respiratory failure, but there was no statistical difference, and long-term chronic hypoxia led to hypothalamic-pituitary-thyroid axis function. A disorder(2) has been associated with a small number of cases in this study. In addition

### Table 4: Comparison of three groups of TSH level.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TSH(±s.mIU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8AM</td>
</tr>
<tr>
<td>Non-respiratory failure</td>
<td>102</td>
<td>1.67±0.81</td>
</tr>
<tr>
<td>I type respiratory failure</td>
<td>51</td>
<td>1.50±0.89</td>
</tr>
<tr>
<td>II type respiratory failure</td>
<td>86</td>
<td>1.28±0.87</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>F组间=1.027,  F组内=38.576, F组间=0.235</td>
<td>P组间=0.360, P组内=0.000, P组间=0.882</td>
</tr>
</tbody>
</table>

### Table 5: Comparison of oxygenation index and APACHE II score in the AECOPD improvement group and death group.

**Note:** Compared with AECOPD improvement group, *P=0.000.*

### Table 6: Logistic multifactor regression analysis of AECOPD patient death risk factors.
to NTIS, there are also circadian rhythm changes of TSH in AECOPD patients, i.e. the loss of peak night secretion of TSH, but there is no difference between the two groups in daytime TSH levels. At the same time, hypoxia, acidosis and carbon dioxide retention have certain effects on the release of TSH, but do not lead to changes in the circadian rhythm of TSH. Although peripheral serum T3 and T4 levels decreased, TSH did not increase reactivity. Moreover, the thyroid hormone can inhibit the secretion of TSH in the pituitary, but has little effect on TSH rhythm and pulsed secretion. Therefore, the disappearance of TSH rhythm in NTIS patients is the result of hypothalamic dysfunction, but not via the negative feedback inhibition of thyroid hormones. It is suggested that the hypothalamic-pituitary-thyroid axis function of AECOPD patients may be damaged.

In 1985, American scholar Knaus first proposed the acute physiology and chronic health evaluation (APACHE II) system\(^7\), which is a widely used quantitative method for evaluating disease severity and predicting death risk at home and abroad. The APACHE II score is directly related to the case fatality rate. An APACHE II score <10 points indicates a lower likelihood of death, the case fatality rate is about 50% at 10-20 points, and the fatality rate is as high as 80% at >20 points\(^{14}\). Studies at home and abroad have shown that the APACHE II score has a high predictive value for the prognosis of patients with AECOPD\(^{15-16}\), and the APACHE II score is an independent risk factor for death in COPD patients with acute respiratory failure in the ICU\(^{17}\). Oxygenation index is the most commonly used indicator for evaluating oxygenation function in clinical practice. Since the United States and Europe Joint Conference established the ALI and ARDS diagnostic criteria in 1994, this standard has been widely used in clinical diagnosis, scientific research and epidemiological studies of ALI and ARDS\(^{18}\). The risk factors for death in COPD patients are positively correlated with oxygenation index, but there is no report on the degree of risk as an independent risk factor\(^{19}\). This study showed that AECOPD patients had a significantly lower oxygenation index and higher APACHE II score in the death group than in the improved group, and the TT3, oxygenation index, and APACHE II scores were independent predictors of AECOPD death. Domestic scholar Liao and others believe that TT3 can be used as an indicator to evaluate the prognosis of patients in the ICU\(^{20}\).

NTIS may be a comprehensive manifestation of the physiological processes of AECOPD, considering the following mechanisms: hypoxia decreases the activity of 5'-deiodinase in peripheral tissues and reduces the transformation from T4 to T3. In addition, stress states such as hypoxia, acidosis and myocardial damage increase the utilisation of T3 in tissues and decrease T3 in blood\(^3\). When infection occurs, body stress promotes activation of the neuroendocrine system, increases the synthesis and secretion of catecholamine, glucocorticoid and cortisol, and inhibits the release of TSH. It also inhibits the transformation of T4 to T3 in peripheral tissues, resulting in the reduction of T3 production\(^{21}\). Hypoxia can cause gastrointestinal congestion and decrease the absorption of iodine by intestinal epithelial cells. In severe hypoxia with cardiac insufficiency, the decrease in renal blood flow and the decrease in iodine reabsorption by renal tubules will aggravate iodine deficiency in vivo, resulting in the decrease of TT3 and TT4\(^3\). AECOPD patients may have increased levels of cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), which further inhibits the synthesis or secretion of TSH, T3 and thyroid peroxidase, thereby reducing serum T3 and T4 concentrations. Infection and hypoxia stress states can cause the decrease of thyroxin-binding globulin levels, affecting the combination of thyroid hormone and thyroid hormone, lowering TT3 and TT4 levels\(^{22}\). When COPD is acutely exacerbated, systemic hormones are often used. Studies have found that the serum T4 level is negatively correlated with oral prednisone dose\(^{23}\). Glucocorticoids may reduce circulating thyroid hormone levels by lowering the serum TSH level, reducing blood vessel and tissue redistribution of T4 and T3, and reducing peripheral T4 to T3 conversion\(^{24}\). Long-term chronic hypoxia leads to disorder of the hypothalamus-pituitary-thyroid axis function and the relative decrease of TSH secretion, thus affecting the synthesis and metabolism of peripheral thyroid hormones\(^2\).

This study found that hypothalamic-pituitary-thyroid axis function may be impaired in AE- COPD patients. In severe AECOPD patients, hypoxia and thyroid hormone levels decreased more significantly. Monitoring serum thyroid hormone levels, oxygenation index and APACHE II scores in the clinic is helpful for judging the severity of disease and evaluating the prognosis.
References


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