Correlates of non-thyroidal illness syndrome in chronic obstructive pulmonary disease

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KEYWORDS
Chronic obstructive pulmonary disease; Thyroid hormones; Non-thyroidal illness syndrome; Interleukin-6; Tumor necrosis factor-alpha

Summary
Non-thyroidal illness syndrome (NTIS) is frequently detected in chronic, systemic diseases. The objectives of the current study is to assess the alterations of thyroid hormones during exacerbation period, recovery of exacerbation and stable phase of chronic obstructive pulmonary disease (COPD) and correlates of these hormonal alterations.
A total of 83 stable COPD patients, 20 patients with acute exacerbation and 30 control subjects were evaluated. TT\textsubscript{3}, fT\textsubscript{3}, TT\textsubscript{3}/TT\textsubscript{4} levels of both stable and exacerbation COPD groups were lower than control subjects. TSH was also decreased during exacerbation period.

In follow-up of COPD exacerbation group, TSH, TT\textsubscript{3}, fT\textsubscript{3} and TT\textsubscript{3}/TT\textsubscript{4} were found to be increased in measurements on the day of discharge from hospital and after 1 month, compared to baseline values.

TT\textsubscript{3} and TT\textsubscript{3}/TT\textsubscript{4} were lower in severe COPD; whereas TSH, fT\textsubscript{3}, TT\textsubscript{3} and TT\textsubscript{3}/TT\textsubscript{4} were lower in patients with severe hypoxemia. IL-6 and TNF-\alpha were higher in both stable and exacerbation phase COPD groups and IL-6 was correlated to TT\textsubscript{3} in stable COPD.
As a result, there are significant alterations in thyroid hormones of stable COPD patients, which are related to severity of disease and hypoxemia. The hormonal changes are more significant during exacerbation and partially regress after 1 month when the disease is stabilized. We conclude that COPD patients should not be evaluated for thyroid disease during exacerbation of the disease, and thyroid function alterations during stable phase of the disease should be considered cautiously, since thyroid function abnormalities in...
Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by significant chronic inflammation not only in the pulmonary compartment, but also in systemic circulation and this disorder is associated with clinically significant systemic alterations in biochemistry and organ function.\(^1\)\(^,\)\(^2\) Several factors such as hypoxemia, exacerbation, drugs, malnutrition may lead to endocrinological changes in COPD.

Alterations in thyroid function tests are common in critical illness, such as starvation, sepsis, surgery, myocardial infarction, and also in chronic, systemic diseases including chronic heart failure, chronic liver or hematologic diseases, cancer, diabetes, connective tissue diseases and COPD.\(^3\) Frequently detected abnormalities of thyroid function in non-thyroidal illness (NTI) are decreased total triiodothyronine (TT3) and free triiodothyronine (FT3), normal or decreased total thyroxine (TT4) and free thyroxine (FT4). Despite these changes, serum thyroid-stimulating hormone (TSH) does not increase and can even be decreased.\(^4\)\(^,\)\(^5\) Low serum TT3 is the most common abnormality in NTI, observed in about 35–70% of hospitalized patients.\(^4\)\(^,\)\(^6\) The terms ”Non-thyroidal Illness Syndrome (NTIS)” and ”Euthyroid Sick Syndrome (ESS)” have been used to describe these abnormalities.

Multiple, complex, usually reversible, and incompletely understood mechanisms are involved in these abnormalities such as disturbances in the hypothalamo–pituitary–thyroid axis, thyroid hormone binding to serum proteins, tissue uptake of thyroid hormones, and/or thyroid hormone metabolism.\(^4\) Evaluation of these abnormalities is necessary for diagnosis of thyroid disease since thyroid function abnormalities in NTI may mimic or mask biochemical abnormalities observed in true thyroid disease. Besides, the severity and nature of these alterations may be a prognostic indicator for the underlying disease. Low serum T3 and/or T4 levels were reported to predict increased mortality from diseases such as cirrhosis and advanced congestive heart failure.\(^7\)\(^,\)\(^8\)

Cytokines were demonstrated to be essential factors in pathogenesis of both acute and chronic diseases. Although the mechanisms underlying NTI are probably multifactorial, these mediators may also be involved in the pathogenesis of NTIS. As a matter of fact, similar thyroid hormone alterations in different underlying diseases have been associated with activation of cytokines.\(^3\) Proinflammatory cytokines, especially IL-6, IL-1β, TNF-α and IFN-γ are important mediators of acute phase of the illness and have inhibiting effects on peripheral thyroid hormone metabolism.\(^5\)\(^,\)\(^9\)\(^,\)\(^10\)

The objectives of the current study are to assess:

(i) alterations of thyroid hormones during exacerbation period, recovery of exacerbation and stable phase of COPD;

(ii) correlates of hormonal alterations and potential role of endogenous cytokines TNF-α and IL-6 in hormonal changes in COPD patients with different degrees of functional impairment and hypoxemia.

Material and methods

Patients

We enrolled 103 consecutive COPD patients who had received a diagnosis of COPD and had received continuing care at our chest clinic and 30 control subjects of the same sex and age group. The diagnosis and severity of COPD had been established by a respiratory physician on the basis of international guidelines.\(^11\) A total of 83 patients had been clinically stable for at least 3 months, and 20 had clinical signs of COPD exacerbation.\(^12\) Clinical criteria used to define an exacerbation were increased dyspnea, sputum production, and sputum purulence. All patients were male and ex-smokers. Stable COPD patients had been receiving inhaled bronchodilator therapy in the form of long-acting β\(_2\) agonists and / or anticholinergic agents. Severe/very severe COPD patients were on inhaled corticosteroids (500–1000 µg budesonide/day). Antibiotics and systemic steroids were added to therapy only in exacerbation period for 10–14 days, after the blood samples were taken. After an overnight fast, anthropometric measurements were made and body mass index (BMI) was calculated. BMI between 19 and 25 was accepted as normal.\(^13\)

Patient exclusion criteria included drug use which may interfere with serum hormone levels such as amiodarone and iodine-containing medication or contrast media, other respiratory or endocrine system diseases, cardiovascular, renal, hepatic, neuromuscular and collagen diseases, malignancy, a known thyroid disease or previous thyroid surgery. Control group consisted of subjects without COPD, acute or chronic illness or drug intake that may alter hormone levels.

The study was approved by the institutional committee on human research and informed consent was obtained from all subjects.

Pulmonary function tests

Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV\(_1\)) were measured with standard spirometric techniques according to the ATS criteria (Minato AutoPal Spirometry, Japan).\(^14\) The highest value from at least three spirometric maneuvers was used. Patients with FEV\(_1\) < 50% of predicted value were considered to have severe/very severe and 50% ≤ FEV\(_1\) < 80% as moderate COPD.\(^15\) Arterial blood sample was obtained while the subjects were breathing room air for at least 30 min, and analyzed with a blood gas analyzer immediately (OMNIC, Roche, Austria).
Thyroid function tests

After medical interview and thyroid examination, serum levels of thyroid hormones (TSH, TT3, TT4, fT3, fT4) were measured using electrochemiluminescence immunoassay (Axysm, Abbott, Germany) and the ratio of TT3/TT4 was calculated (normal limits for thyroid function tests: TSH:0.49–4.67; TT3:0.45–1.37; TT4:4.5–12; fT3:1.45–3.48; fT4:0.71–1.89). Thyroid hormones were measured once in stable COPD patients and controls, and measured thrice in COPD exacerbation group; on the first day of hospitalization (before systemic steroids or antibiotics were given), on the day of discharge from hospital (after 10–14 days of treatment) and after 1 month.

Cytokine assays

Fasting blood samples (~10ml) were collected by venipuncture into plain tubes. Sera were obtained by centrifugation at 1000g for 5 min at room temperature. The samples were stored at –70°C until analysis.

Serum TNF-α concentration (pg/ml) was measured by a solid phase sandwich ELISA using hTNF-α kit (BioSource International Inc., California, USA). Serum IL-6 concentration (pg/ml) was also measured by enzyme-linked immunosorbent assay (ELISA) kits (Biosource International Inc., California, USA).

Statistical analysis

Data were presented as mean value ± standard deviation of the mean. Correlations between parameters were evaluated using “Pearson” rank correlation analysis. Nonparametric data of study groups were compared by “Mann–Whitney U test”. “One-way analyses of variance” was used to compare differences in COPD subgroups. “Friedman” test was used to compare baseline and subsequent control hormone levels of COPD patients. Significance was determined at 5% level.

Results

Pulmonary function tests and arterial blood gases

Characteristics and pulmonary function tests of COPD patients and control subjects admitted to the study are shown in Table 1.

Thyroid function tests

Among 83 stable COPD patients, thyroid hormones of 25 were not within normal limits. Further diagnostic investigations revealed toxic multinodular goitre in 3, Hashimoto’s thyroiditis in 2, toxic adenoma in 2 and silent thyroiditis in 1 patient. These 8 patients were excluded from further analyses and the remaining 17 patients (20%) were evaluated as NTIS (Table 2).

Thyroid hormones of 18 exacerbation phase COPD patients were not within normal limits. Of these, 3 were diagnosed as toxic multinodular goitre and 1 as Hashimoto’s thyroiditis. These 4 patients were excluded from further analyses and the remaining 14 patients (70%) were evaluated as NTIS (Table 2). Thyroid hormone abnormalities regarded as NTIS in both groups are given in Table 3.
Toxic multinodular goitre was detected in 1 subject in control group. Thyroid hormones were within normal limits in rest of them.

Thyroid hormone levels of the entire COPD group, stable and exacerbation period COPD patients and control subjects are shown in Table 4. Serum TT3, fT3 and TT3/TT4 of stable COPD patients were lower than controls. In exacerbation group, TSH was also lower besides TT3, fT3 and TT3/TT4. When stable and exacerbation COPD groups were compared, TT3, fT3 and TT3/TT4 were found lower in exacerbation period. Taken together, TT3 and especially fT3 were lower in COPD patients, and the alterations became more significant during acute exacerbation of the disease.

In follow-up of COPD exacerbation group, TSH, TT3, fT3 levels and TT3/TT4 ratio were found to be increased in measurements on the day of discharge from hospital and after 1 month, compared to baseline values (Table 5). Follow-up arterial blood gas analyses also revealed significant changes in PaO2 and PaCO2 (Table 5). Hormonal alterations improved as the arterial blood gas values improved during recovery period of exacerbation.

Serum thyroid hormone levels of moderate (FEV1 > 50) and severe (FEV1 < 50) COPD patients were given in Table 6. TT3 and TT3/TT4 were lower in severe COPD compared to moderate COPD, indicating that the degree of hormonal alterations may be a marker of severity of the disease.

Thyroid hormones of COPD patients with moderate (80 > PaO2 ≥ 60 mmHg) and severe hypoxemia (PaO2 < 60 mmHg) were shown in Table 7. TSH, TT3, fT3 levels were lower in patients with severe hypoxemia. There was no difference between thyroid hormones of hypercapnic (PaCO2 > 45 mmHg) and normocapnic (PaCO2 ≤ 45 mmHg) patients (p > 0.05 for all parameters).

BMI of COPD patients was lower than control subjects (Table 1, p = 0.042). Serum TSH was lower in COPD patients with low (<19) BMI (p = 0.008).

**Cytokine assays**

Serum IL-6 and TNF-α levels in COPD patients and control subjects are given in Table 4. IL-6 and TNF-α concentrations were higher in both stable and exacerbation phase COPD groups than controls.

**Correlations**

In correlation tests of stable COPD patients, there was no correlation between thyroid hormones and burden of smoking or BMI. There was negative correlation between age and TT3 (r = −0.028, p = 0.038), fT3 (r = −0.278, p = 0.011) and TT3/TT4 (r = −0.236, p = 0.032). There was positive correlation between pH and TSH (r = 0.255, p = 0.020) and PaO2 and TT3 (r = 0.206, p = 0.048), and negative correlation between PaCO2 and TSH (r = −0.229, p = 0.038). In COPD exacerbation group, there was positive correlation between PaO2 and fT4 (r = 0.450, p = 0.046). In stable COPD group, IL-6 was correlated to TT3 (r = 0.712,

### Table 3 Thyroid hormone abnormalities evaluated as NTIS in stable and exacerbation phase COPD groups (patients with thyroid disease are not included).

<table>
<thead>
<tr>
<th></th>
<th>Stable COPD (n = 17)</th>
<th>Exacerbation (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ TSH</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>↓ TT3</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>↓ fT3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>↓ TT4</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>↓ TSH/ ↓ TT3</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>↓ TT3/ ↓ fT3</td>
<td>–</td>
<td>2</td>
</tr>
</tbody>
</table>

COPD, Chronic obstructive pulmonary disease; NTIS, Non-thyroidal illness syndrome.

### Table 4 Serum thyroid hormones, IL-6 and TNF-α levels in COPD patients (entire group, stable and exacerbation subgroups) and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Stable</th>
<th>Exacerbation</th>
<th>Controls</th>
<th>p*</th>
<th>p**</th>
<th>p***</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.96 ± 0.41</td>
<td>1.07 ± 1.04</td>
<td>0.51 ± 0.48</td>
<td>0.83 ± 0.49</td>
<td>0.716</td>
<td>0.030</td>
<td>0.008</td>
</tr>
<tr>
<td>TT3</td>
<td>0.94 ± 0.41</td>
<td>0.95 ± 0.43</td>
<td>0.87 ± 0.32</td>
<td>1.12 ± 0.49</td>
<td>0.007</td>
<td>0.011</td>
<td>0.123</td>
</tr>
<tr>
<td>TT4</td>
<td>8.66 ± 2.33</td>
<td>8.50 ± 1.85</td>
<td>9.33 ± 3.72</td>
<td>8.25 ± 1.77</td>
<td>0.815</td>
<td>0.699</td>
<td>0.653</td>
</tr>
<tr>
<td>fT3</td>
<td>2.27 ± 0.68</td>
<td>2.28 ± 0.41</td>
<td>2.21 ± 1.32</td>
<td>3.05 ± 2.07</td>
<td>0.000</td>
<td>0.001</td>
<td>0.015</td>
</tr>
<tr>
<td>fT4</td>
<td>1.11 ± 0.40</td>
<td>1.05 ± 0.21</td>
<td>1.34 ± 0.78</td>
<td>1.13 ± 0.22</td>
<td>0.136</td>
<td>0.599</td>
<td>0.075</td>
</tr>
<tr>
<td>TT3/TT4</td>
<td>0.12 ± 0.54</td>
<td>0.11 ± 0.58</td>
<td>0.09 ± 0.26</td>
<td>0.14 ± 0.84</td>
<td>0.010</td>
<td>0.001</td>
<td>0.044</td>
</tr>
<tr>
<td>IL-6</td>
<td>70.57 ± 117.16</td>
<td>68.86 ± 50.42</td>
<td>71.40 ± 130.16</td>
<td>24.77 ± 47.23</td>
<td>0.012</td>
<td>0.019</td>
<td>0.802</td>
</tr>
<tr>
<td>TNF-α</td>
<td>13.14 ± 32.58</td>
<td>11.43 ± 11.91</td>
<td>14.87 ± 36.03</td>
<td>5.99 ± 5.29</td>
<td>0.033</td>
<td>0.034</td>
<td>0.449</td>
</tr>
</tbody>
</table>

*p value is obtained by comparison of stable COPD patients and control subjects.

**p value is obtained by comparison of COPD exacerbation group and control subjects.

***p value is obtained by comparison of stable and exacerbation groups of COPD patients.

COPD, Chronic obstructive pulmonary disease; TSH, Thyroid-stimulating hormone (μIU/ml); TT3, Total triiodothyronine (ng/ml); TT4, Total thyroxine (μg/dl); fT3, Free triiodothyronine (pg/ml); fT4, Free thyroxine (ng/dl); IL-6, Interleukin-6 (pg/ml); TNF-α, Tumor necrosis factor-alpha (pg/ml).
Discussion

Non-thyroidal illness syndrome may be regarded as an acute phase response of the organism that serves as one of the major mechanisms of the body to restore homeostasis in severe illness. Alterations in circulating thyroid hormone concentrations have been reported in several acute and/or chronic disease states. However, limited information exists on thyroid function in COPD, since most studies have been performed on small series of patients and mainly on those with severe disease, usually without a control group. Extensive investigation of the mechanisms leading to alterations in thyroid hormone metabolism seen in NTI has failed to identify a single factor responsible for the observed changes. It is likely that multiple factors determine these characteristic changes in thyroid hormone metabolism. In NTI, there is evidence for interference of normal hypothalamic-pituitary-thyroid axis function, as well as altered peripheral thyroid hormone transport and metabolism.

Among previous studies, Semple et al. measured serum TT3 and TT4 levels in 16 stable patients with severe COPD and did not detect difference among hypercapnics, normocapnics and controls. The same investigators performed thyroid stimulation tests in 8 hypoxic, stable patients with severe COPD in a subsequent study and found that their basal thyroid hormone levels were normal, but 2 patients showed a delayed response to TRH. They concluded that hypoxemia causes a minor change in the hypothalamic–pituitary–thyroid axis function, as well as altered peripheral thyroid hormone transport and metabolism.

Banks et al. measured thyroid hormones of 25 COPD patients with various degrees of hypoxemia and hypercapnia. There was no relation between thyroid hormones and pH, PaO2 or PaCO2 but there was an inverse correlation between serum thyroxine and daily dose of oral prednisolone. They concluded that several endocrinological alterations secondary to chronic pulmonary diseases might be related to factors other than hypoxia and hypercapnia. In the present study, there was no patient on regular systemic steroids. Systemic steroids were added to therapy only in exacerbation period, but baseline blood samples were taken before the therapy.

Dimiopoulos et al. demonstrated that serum thyroid hormone levels were within normal limits in 46 COPD patients with stable, mild-to-severe disease but they did not have a control group to compare the results. While there

### Table 5 Baseline, 1. control and 2. control thyroid hormone levels and blood gas analyses of COPD exacerbation patients.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1. control</th>
<th>2. control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.52 ± 0.48</td>
<td>0.66 ± 0.63</td>
<td>1.22 ± 1.36</td>
<td>0.000</td>
</tr>
<tr>
<td>TT3</td>
<td>0.88 ± 0.33</td>
<td>0.76 ± 0.40</td>
<td>0.96 ± 0.29</td>
<td>0.041</td>
</tr>
<tr>
<td>TT4</td>
<td>9.33 ± 3.72</td>
<td>8.70 ± 3.46</td>
<td>8.04 ± 2.22</td>
<td>0.084</td>
</tr>
<tr>
<td>FT3</td>
<td>2.21 ± 1.32</td>
<td>2.18 ± 1.60</td>
<td>2.80 ± 0.68</td>
<td>0.001</td>
</tr>
<tr>
<td>FT4</td>
<td>1.34 ± 0.78</td>
<td>2.22 ± 3.79</td>
<td>1.15 ± 0.32</td>
<td>0.963</td>
</tr>
<tr>
<td>TT3/TT4</td>
<td>0.09 ± 0.26</td>
<td>0.21 ± 0.28</td>
<td>0.19 ± 0.21</td>
<td>0.043</td>
</tr>
<tr>
<td>PH</td>
<td>7.40 ± 0.04</td>
<td>7.39 ± 0.05</td>
<td>7.41 ± 0.02</td>
<td>0.188</td>
</tr>
<tr>
<td>PaO2</td>
<td>70.35 ± 13.23</td>
<td>72.36 ± 7.57</td>
<td>76.81 ± 7.15</td>
<td>0.036</td>
</tr>
<tr>
<td>PaCO2</td>
<td>43.37 ± 8.99</td>
<td>45.27 ± 10.31</td>
<td>39.60 ± 5.11</td>
<td>0.000</td>
</tr>
</tbody>
</table>

COPD, Chronic obstructive pulmonary disease; TSH, Thyroid-stimulating hormone (μIU/ml); TT3, Total triiodothyronine (ng/ml); TT4, Total thyroxine (μg/dl); FT3, Free triiodothyronine (pg/ml); FT4, Free thyroxine (ng/dl); PaO2, Oxygen partial pressure (mmHg); PaCO2: Carbondioxide partial pressure (mmHg).

### Table 6 Thyroid hormones of moderate and severe COPD patients.

<table>
<thead>
<tr>
<th></th>
<th>Moderate COPD</th>
<th>Severe COPD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.94 ± 0.94</td>
<td>0.97 ± 1.00</td>
<td>0.842</td>
</tr>
<tr>
<td>TT3</td>
<td>1.08 ± 0.66</td>
<td>0.88 ± 0.23</td>
<td>0.018</td>
</tr>
<tr>
<td>TT4</td>
<td>8.68 ± 1.96</td>
<td>8.65 ± 2.48</td>
<td>0.650</td>
</tr>
<tr>
<td>FT3</td>
<td>2.34 ± 0.39</td>
<td>2.24 ± 0.77</td>
<td>0.085</td>
</tr>
<tr>
<td>FT4</td>
<td>1.08 ± 0.24</td>
<td>1.12 ± 0.45</td>
<td>0.928</td>
</tr>
<tr>
<td>TT3/TT4</td>
<td>0.13 ± 0.08</td>
<td>0.10 ± 0.02</td>
<td>0.037</td>
</tr>
</tbody>
</table>

COPD, Chronic obstructive pulmonary disease; Moderate COPD, Forced expiratory volume in 1 s (FEV1) >50%; Severe COPD, FEV1<50%.

### Table 7 Thyroid hormones of COPD patients with moderate and severe hypoxemia.

<table>
<thead>
<tr>
<th></th>
<th>Moderate hypoxemia</th>
<th>Severe hypoxemia</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>1.02 ± 0.90</td>
<td>0.85 ± 1.13</td>
<td>0.048</td>
</tr>
<tr>
<td>TT3</td>
<td>1.00 ± 0.47</td>
<td>0.81 ± 0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>TT4</td>
<td>8.85 ± 2.38</td>
<td>8.24 ± 2.24</td>
<td>0.163</td>
</tr>
<tr>
<td>FT3</td>
<td>2.38 ± 0.75</td>
<td>2.04 ± 0.47</td>
<td>0.015</td>
</tr>
<tr>
<td>FT4</td>
<td>1.12 ± 0.45</td>
<td>1.09 ± 0.30</td>
<td>0.614</td>
</tr>
<tr>
<td>TT3/TT4</td>
<td>0.11 ± 0.06</td>
<td>0.10 ± 0.03</td>
<td>0.295</td>
</tr>
</tbody>
</table>

COPD, Chronic obstructive pulmonary disease; Moderate hypoxemia, 80 >PaO2 ≥ 60 mmHg; Severe hypoxemia, PaO2 < 60 mmHg.

p = 0.000) and TT3/TT4 (r = 0.692, p = 0.000); however there was no correlation between other hormone parameters and TNF-α or IL-6 in both groups.
was no correlation between TT3, TT4, TT3/TT4 and study parameters in patients with FEV1 ≥ 50% predicted; there was strong positive correlation between TT3/TT4 ratio and PaO2 in patients with FEV1 < 50%. They concluded that severity of disease through hypoxemia is important in determining the peripheral metabolism of thyroid hormones.

Okutan et al.19 evaluated the relation between thyroid hormones and pulmonary function in moderate-to-severe COPD. Thyroid hormone concentrations of COPD patients were within normal limits, but FT3 was lower in COPD group than controls. Besides, there was a negative correlation between pulmonary function tests, PO2 and FT3 in COPD patients.

In the present study, we evaluated 103 moderate-to-severe COPD patients (mean FEV1 44%) and 30 controls with normal pulmonary function. We found TT3 and FT3 levels and TT3/TT4 ratio were lower in COPD group than controls and the difference was more significant for FT3. Besides, there was significant difference in TSH, TT3, fT3 levels and TT3/TT4 ratio of stable and exacerbation groups. When we evaluated the relation between pulmonary function tests and thyroid hormones, we found out that serum TT3 and TT3/TT4 ratio were lower in severe COPD compared to moderate COPD.

TSH, TT3, fT3 levels were lower in patients with severe hypoxemia (PaO2 < 60 mmHg) when compared to patients with milder hypoxia. We observed that FT4 decreased parallel to PaO2 in exacerbation period. The decrease in T3, fT3 and TT3/TT4 while T4 remains stable in patients with severe airflow obstruction and patients in exacerbation period with severe hypoxemia support the above-mentioned studies indicating that hypoxemia and severity of COPD affect peripheral metabolism of thyroid hormones. On the other side, the degree of alteration in TT3 level may be a useful marker of severity and prognosis of COPD, which remains to be clarified by further studies.

We did not detect difference between thyroid hormones of patients with and without hypercapnia. However, there was inverse correlation between TSH and PaCO2 in stable COPD group. That is why we consider hypercapnia may play role in thyroid dysfunction besides hypoxemia.

We demonstrated that TSH, TT3, fT3 levels and TT3/TT4 ratio were lower than control subjects in 20 patients with COPD exacerbation (mean FEV1 < 36% and mean ratio were lower than control subjects in 20 patients with COPD). Thay is why we consider hypercapnia may play role in thyroid dysfunction besides hypoxemia. As a matter of fact, Blum et al. evaluated thyroid function in geriatric patients (mean age 83 ± 6) and detected that TT3 was lower and FT4 was higher in aged people.10

Decrease in BMI due to systemic inflammation and oxidative stress was reported in COPD.21 BMI was lower in COPD group than controls in our study. Serum TSH was found to be lower in patients with low BMI compared to patients with normal-to-high BMI, indicating that malnutrition may also be related to hormonal changes in COPD.

The alterations in thyroid hormones in COPD might also be related to factors other than hypoxia and hypercapnia. TNF-α was demonstrated to be a mediator of several diseases leading to hypothalamo–pituitary dysfunction. Investigation of the effects of administering TNF-α and IL-1β to experimental animals and humans confirmed a possible role for them in the pathogenesis of NTIS, with each cytokine inducing critical illness and changes of low serum T39,22–24 Both cytokines also induce IL-6 production.3 IL-6 is known to exert regulatory effects upon many endocrine systems, either independently, or acting with other cytokines.5,10,25 Stouthard et al. evaluated the effect of IV IL-6 administration on thyroid hormone metabolism in humans.10 IL-6 administration induced an acute decrease in T3 and TSH. However, during prolonged sc administration of IL-6, these effects seemed to be transient. After 1 week of daily administration of IL-6, thyroid hormones returned to baseline values. Therefore they concluded that acute elevations of IL-6 may at least in part mediate the development of the NTIS, whereas factors other than IL-6 contribute to the persistence of changes in thyroid hormone concentrations during chronic illness.

Davies et al. demonstrated a relation between elevated serum IL-6 concentrations and alterations in circulating thyroid hormones in NTI secondary to various medical conditions.6 In the present study serum IL-6 and TNF-α concentrations were higher in both COPD groups than controls. In stable COPD group, IL-6 was correlated to TT3, however there was no correlation between other hormone parameters and TNF-α or IL-6 in both groups. Indeed, the role of TNF-α in NTIS is controversial. Although TNF-α has been shown to play role in NTIS in several experimental studies, there is also opposite data. Boelen et al. showed that immunoneutralization of IL-1, TNF-α or IFN-γ did not prevent NTIS in mice; however, immunoneutralization of IL-6 transiently inhibited decrease of 5’-deiodinase.26 Similarly, Chopra et al. studied TNF-α concentration in NTI and found in normal range.27 They did not detect correlation between TNF-α and thyroid hormones and concluded that TNF-α is not a universal or common factor in the pathogenesis of NTIS.

There is no adequate data on the prevalence of thyroid dysfunction in COPD. Among 270 NTI patients (liver, renal, cardiac disease and general medical or surgical conditions) 35% had a serum T3 below the normal range and 33% had serum T4 below the normal range.6 The prevalence of NTIS was reported as 18% in 199 patients with moderate-to-severe congestive heart failure.28 We established NTIS in 17 of 83 (20%) stable COPD patients. Further studies are needed to estimate the prevalence of thyroid dysfunction in COPD.

It is not clear if these patients with NTIS are metabolically euthyroid or not. A normal serum TSH in most NTIS patients with low T3 may indicate that they are metabolically...
hormone replacement therapy. However, studies evaluating patients with NTI may be euthyroid because of short increase in serum TSH during recovery from NTI suggests adaptation and these patients are indeed biochemically catabolism and protein breakdown; or is an unfavourable observed in true thyroid disease. Whether NTIS in COPD is a thyroid illness may mimic or mask biochemical abnormalities cautiously, since thyroid function abnormalities in non-bation of the disease, and thyroid function alterations should not be evaluated for thyroid disease during exacer-

and turnover of thyroid hormones.

As a conclusion, as there are significant alterations in thyroid hormones of COPD patients, we suggest that they should not be evaluated for thyroid disease during excer-bation of the disease, and thyroid function alterations during stable phase of the disease should be considered cautiously, since thyroid function abnormalities in non-
thyroid illness may mimic or mask biochemical abnormalities observed in true thyroid disease. Whether NTIS in COPD is a useful compensatory mechanism to counteract excessive catabolism and protein breakdown; or is an unfavourable adaptation and these patients are indeed biochemically hypothyroid, and will benefit from thyroid hormone replace-
ment therapy remains to be clarified by further studies.

References


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