Effects of Severity of Chronic Obstructive Pulmonary Disease on Thyroid Function

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To investigate thyroid function in chronic obstructive pulmonary disease (COPD), 46 consecutive patients (35 men) with stable, mild-to-severe disease, having a mean (SD) age of 67 ± 7 years were studied. All subjects underwent pulmonary function tests (PFTs), arterial blood gas determination, and measurement of serum total thyroxine (TT4), total triiodothyronine (TT3), resin T3 uptake (RT3U), reverse triiodothyronine (rT3), and thyroid-stimulating hormone (TSH) levels. The free thyroxine and free triiodothyronine indexes (FT4I = RT3U/30TT4 and FT3I = RT3U/30TT3, respectively) along with the TT3/TT4 ratio were calculated; the latter was used as a marker of peripheral conversion of thyroxine into triiodothyronine. Interleukin (IL)-6 was also measured to evaluate its potential associations with thyroidal hormone levels. On the basis of forced expiratory volume in 1 second (FEV_1), patients were divided in 2 groups: group 1, ($FEV_1 \geq 50\%$ of predicted, n = 26), with mild-to-moderate COPD and group 2 ($FEV_1 < 50\%$ of predicted, n = 20) having severe disease. All subjects had normal serum thyroid hormone levels; for the entire COPD population, mean values were 7.80 ± 1.60 μg/dL for TT4, 1.12 ± 0.20 ng/mL for TT3, 29.0 ± 1.88 for RT3U, 7.54 ± 1.34 for FT4I, 1.07 ± 0.16 for FT3I, 18.71 ± 5.89 ng/dL for rT3, and 1.15 ± 0.6 μU/mL for TSH. Mean TT3/TT4 ratio was 0.14 ± 0.03. In group 1, TT3, TT4, and TT3/TT4 ratio did not correlate with age, FEV_1, PaO_2, or inhaled corticosteroids. Similarly, in group 2, TT3 and TT4 were unrelated to the above-mentioned variables; however, there was a strong positive correlation between TT3/TT4 ratio and PaO_2 ($r = .61$, $P = .004$). IL-6 was within normal limits in all subjects, and it did not correlate with any thyroid hormone either in group 1 or in group 2. It is concluded that in stable COPD, severity of disease through hypoxemia is important in determining the peripheral metabolism of thyroid hormones. Whether this constitutes an adaptation is not known.

ABNORMALITIES IN THYROID hormone regulation are encountered frequently in nonthyroidal illness (NTI); these include normal or decreased total and free thyroxine (TT4 and FT4 respectively), decreased total (TT3) and free (FT3) triiodothyronine along with usually normal thyroid-stimulating hormone (TSH) levels. These changes have been observed primarily in critical illness, such as starvation, sepsis, surgery, or myocardial infarction,[1,2] but also in diverse chronic, systemic conditions, ie, in chronic heart failure,[3] chronic liver or hematologic diseases, cancer, diabetes,[2,4] and in connective tissue disorders.[5] Furthermore, serum hormone levels have been found to closely correlate with severity of the underlying condition, both in acute and chronic situations.[1,3]

Thyroid function in chronic obstructive pulmonary disease (COPD) has not been extensively investigated. Previous studies have focused primarily either on patients during acute exacerbations or only on those with severe airflow limitation. These studies demonstrated absent or delayed TSH responses to administered thyrotropin-releasing hormone (TRH) in a small number of subjects, suggesting a certain degree of thyroid dysfunction in COPD.[6,7]

The uniform expression of thyroid hormone alterations in NTI despite the heterogenous nature of the underlying diseases has been associated with the activation of the inflammatory cytokine system.[4,8] Tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1, being proinflammatory mediators, induce the release of IL-6 from monocytes/macrophages, and all 3 have been shown to modulate thyroid hormone metabolism in vivo and in vitro.[9,10] Moreover, IL-6 serum levels have been shown to be strongly inversely correlated with both TT3 and the TT3/TT4 ratio in children with NTI.[11,12]

To further clarify thyroid function in COPD, we studied a large number of stable patients, having a wide range in degree of airflow obstruction. The objectives of the current study were to assess the occurrence of thyroid dysfunction, investigate factors determining thyroid function in COPD patients having different degrees of functional impairment, and examine the potential associations between IL-6 and thyroidal hormone levels in such subjects. Thyroid function was studied by measuring serum concentrations of TT4, TT3, resin T3 uptake (RT3U), reverse triiodothyronine (rT3), and TSH levels, and by calculating the free thyroxine and free triiodothyronine indexes (FT4I and FT3I, respectively) along with the TT3/TT4 ratio; this ratio was used to examine the peripheral conversion of thyroxine into the metabolically active thyroid hormone, T3.

MATERIALS AND METHODS

Patients

Forty-six consecutive patients (35 men) with stable COPD, having a mean (SD) age of 67 ± 7 years were enrolled in the present study. Inclusion criteria for COPD were those of the European Respiratory Society consensus statement[13]: (1) symptoms of chronic bronchitis, defined by the presence of chronic or recurrent increases in bronchial secretions, present on most days for a minimum of 3 months a year, for at least 2 consecutive years, not attributed to any other pulmonary or cardiac disease; (2) evidence of airway obstruction, ie, forced expiratory volume in 1 second (FEV_1) less than 80% of predicted and reduced FEV_1 to forced vital capacity (FEV_1/FVC) ratio; (3) no improvement in FEV_1 of more than 10% after inhalation of 200 μg salbutamol. Exclu-

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sion criteria were: (1) treatment with oral glucocorticoids or with any other drug known to affect thyroid function, such as amiodarone or iodine-containing contrast media[2] (2) recent (within the last 3 months) acute exacerbation; (3) clinical evidence of thyroid disease; (4) coexistence of other diseases altering thyroid function tests.[1,2] All patients were current or ex-smokers. Of the 46 patients, 38 were receiving bronchodilators, which consisted of inhaled β_2 agonists (37 patients), inhaled anticholinergics (19 patients), and/or oral theophylline (15 patients). Twenty-five patients were on anti-inflammatory drugs (inhaled corticosteroids); 10 patients received budesonide, 8 fluticasone, and 7 beclomethasone. The mean dose of inhaled corticosteroids was 924 ± 457 μg/d (range, 400 to 2,000 μg/d). Only 1 patient was on 2,000 μg/d, while the maximum dose in the remaining patients was 1,500 μg/d. Nutritional status was adequate, mean body mass index (BMI) being 25.7 ± 3.4 kg/m^2.

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

Protocol

Pulmonary function tests. Pulmonary function tests (PFTs) (spirometry and flow-volume loop) were performed on a MasterScreen Diffusion system (E. Jaeger, Wuerzburg, Germany). Spirometric indices were calculated from the best of 3 satisfactory efforts, defined as the effort associated with the highest sum of FVC and FEV_1. Both FVC and FEV_1 were expresseed as percent of the predicted according to the European Guidelines.[13]

On the basis of FEV_1, patients were divided in 2 groups: group 1, with an $FEV_1 \geq 50\%$ of predicted, having mild-to-moderate COPD, and group 2, with an FEV_1 less than 50% of predicted, having severe COPD.

Arterial blood gases. Arterial blood was obtained from the radial artery while patients were breathing room air for at least 30 minutes, and the samples were analyzed for PaO_2, $PaCO_2$, and pH with a blood gas analyzer (Ciba Corning 238 pH/Blood Gas Analyzer; Ciba Corning Diagnostics Ltd, Essex, UK).

Thyroid function assays. Serum levels of TT4 (sensitivity, 0.03 μg/dL; interassay coefficient of variation [CV], 3.6% to 4.7%; intra-assay CV, 2.6% to 3.2%; normal values, 5 to 12.8 μg/dL) and TT3 (sensitivity, 0.10 ng/mL; interassay CV, 3.2% to 4.9%; intra-assay CV, 1.6% to 3.7%; normal values, 0.5 to 1.75 ng/mL) were measured by radioimmunoassay methods (Amerlex-M; Ortho-Clinical Diagnostics, Amersham, UK). Measurement of serum TSH was performed with an immunoradiometric assay (Clinical Assay Gammacoat hTSH ^{125}I IRMA Kit; Incstar, Stillwater, MN; sensitivity, 0.01 μIU/mL; interassay CV, 4.0% to 5.7%; intra-assay CV, 3.1% to 3.3%; normal values, 0.30 to 3.70 μIU/mL). Reverse T3 was measured with radiommunoassay (rT3 RIA; Biocode Biotechnology, Liège, Belgium; sensitivity, 0.5 ng/dL; interassay CV, 3.9% to 6.9%; intra-assay CV, 3.0% to 6.1%; normal values, 15 to 35 ng/dL). The resin T3 uptake (RT3U) was determined with our in-house assay (interassay CV, 1.4% to 1.9%; intra-assay CV, 1.2% to 1.8%) described elsewhere.[14] The FT4I (= RT3U/30TT4, normal values 5.0 to 12.8), the FT3I (= RT3U/30TT3, normal values, 0.5 to 1.75), and the ratio of TT3 to TT4 (TT3/TT4) were calculated.

Cytokine assays. Serum IL-6 was measured with an enzymoimmunometric assay (Quantikine HS human IL-6 immunoassay; R&D Systems, Oxon, England; sensitivity, 0.094 pg/mL; interassay CV, 6.7% to 29.5%; intra-assay CV, 3.8% to 11.1%; normal values, 0.38 to 10.10 pg/mL). All blood samples were obtained on the same day with PFTs.

Statistical analysis. Data are presented as mean value ± standard deviation of the mean unless otherwise stated. The normalcy of the distributions of the measured or calculated variables was validated with the Kolmogorov-Smirnov test. Comparisons between group 1 and group 2 patients were performed by using unpaired *t* test, Fisher exact, or χ^2 analysis where appropriate. The relationships between the various parameters were assessed separately in group 1 and group 2 patients by computing Pearson Product-Moment correlation coefficients. Bonferroni correction for multiple correlations was applied, thus setting statistical significance at $P \approx .004$.[15] All analyses were performed using a commercial software package (Sigmastat; Jandel, San Rafael, CA).

RESULTS

PFTs and Arterial Blood Gases

For the entire group of COPD patients, mean values for FVC, FEV_1, and FEV_1/FVC were 75% ± 18% of predicted, 53% ± 18% of predicted, and 54% ± 12%, respectively. In all, except 2 patients, FEV_1/FVC ratio was below 70%; in these 2 subjects, FEV_1 was below 80% of predicted, suggesting mild airway obstruction. FEV_1 increased by 5 ± 1% following inhalation of a bronchodilator. Regarding arterial blood gases, COPD patients as a group had mildly reduced PaO_2 levels (mean PaO_2 = 73 ± 18 mm Hg), but $PaCO_2$ was within normal limits (mean $PaCO_2$ = 42 ± 5 mm Hg). Three subjects had respiratory failure (PaO_2, 56, 57, and 59 mm Hg, respectively), and 10 had mild hypercapnia ($PaCO_2$ range, 46 to 53 mm Hg).

There were 26 patients in group 1 (mild-to-moderate COPD) and 20 subjects in group 2 (severe COPD). The 2 groups were well matched for age, gender, smoking habits, and inhaled corticosteroids (Table 1). Although there were no significant differences in height and weight in our 2 groups of COPD patients, group 1 patients had a higher BMI compared with group 2 patients. Taking BMI into consideration, both groups were classified as overweight, but not obese. Results of PFTs and arterial blood gases for the 2 groups are given in Table 2. As expected, group 2 patients had significantly lower values for FVC, FEV_1, and FEV_1/FVC ratio. Mean $PaCO_2$ was higher in group 2 patients, but PaO_2 was comparable in the 2 groups.

Thyroid Function Tests

In all patients TT4, TT3, TSH, FT4I, FT3I, and rT3 levels were within normal limits; mean values and corresponding ranges for the entire group of COPD subjects are shown in Table 3. Mean calculated serum TT3/TT4 ratio was 0.14 ± 0.03 (range, 0.09 to 0.21).

In group 1 patients, there were no significant correlations between TT4 levels and age (r = .08, P = .60), FEV_1% of predicted (r = .02, P = .90), PaO_2 (r = .21, P = .16), or inhaled corticosteroids (r = .04, P = .76). Similarly, TT3 and TT3/TT4 ratio did not correlate significantly with the above-

Table 1. Patient Characteristics According to Severity of COPD

	Group 1, n = 26 ($FEV_1 \geq 50\%$ pred)	Group 2, n = 20 ($FEV_1 < 50\%$ pred)	*P* Value
Age (yr)*	67 ± 6	68 ± 8	NS
Gender (M/F) (n)	19/7	16/4	NS
Ex/current smokers (n)	26	20	NS
Weight (kg)*	76 ± 11	70 ± 14	NS
Height (cm)*	162 ± 7	163 ± 7	NS
BMI (kg/m^2)*	28.8 ± 3.3	26.0 ± 4.2	.02
Inhaled steroids (n)	16	11	NS

* Mean ± SD.

Abbreviation: NS, nonsignificant.

Table 2. PFTs and Arterial Blood Gases According to Severity of COPD

Variable	Group 1, n = 26 ($FEV_1 \geq$ 50% pred)	Group 2, n = 20 ($FEV_1 <$ 50% pred)	*P* Value
FVC (% pred)	86 ± 14	61 ± 13	<.001
FEV_1 (% pred)	66 ± 9	35 ± 10	<.001
FEV_1/FVC (%)	61 ± 9	45 ± 11	<.001
PaO_2 (mm Hg)	75 ± 8	71 ± 9	.10
$PaCO_2$ (mm Hg)	40 ± 4	44 ± 5	.002
pH	7.42 ± 0.03	7.41 ± 0.03	.33

NOTE. Mean ± SD.

Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, forced expiratory volume in 1 second to forced vital capacity ratio; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension.

mentioned variables. The correlations of BMI versus PaO_2 (r = -.43, P = .03) and TT3/TT4 (r = -.17, P = .40) were also nonsignificant.

In group 2 patients, there were no significant correlations between TT4 or TT3 and age, FEV_1, PaO_2, or inhaled corticosteroids. In contrast, a highly significant positive correlation between TT3/TT4 ratio and PaO_2 was found (r = .61, P = .004) (Fig 1). TT3/TT4 did not correlate with age, PFTs, or inhaled steroids. Similarly, there was no relationship between BMI and PaO_2 or TT3/TT4.

Cytokine Assays

IL-6 was not normally distributed. Median IL-6 was at 3.30 pg/mL, lower and upper quartiles were at 2.00 and 5.30 pg/mL, respectively, while minimum and maximum values were at 1.20 and 100.00 pg/mL, respectively. IL-6 was not significantly correlated to any thyroid hormone studied, neither in group 1 nor group 2.

DISCUSSION

We sought to investigate thyroid function in patients with stable COPD, presenting a spectrum in disease severity, as indicated by the various degrees of airway obstruction. We found that all of our subjects had normal values for resting thyroid hormones. However, in severe COPD, a certain degree of thyroid dysfunction was evident, ie, the peripheral conversion of thyroxine into the principal biologically active hormone, triiodothyronine, was a function of oxygenation level.

Alterations in circulating thyroid hormone concentrations

Table 3. Thyroid Function Tests in all COPD Patients (n = 46)

Variable	Mean ± SD	Range
TT4 (μg/dL)	7.80 ± 1.60	5.30-11.90
TT3 (ng/mL)	1.12 ± 0.20	0.64-1.66
TSH (μIU/mL)	1.15 ± 0.6	0.22-3.10
FT4I	7.54 ± 1.34	5.20-10.70
FT3I	1.07 ± 0.16	0.67-1.43
rT3 (ng/dL)	18.71 ± 5.89	10.70-36.40

Abbreviations: TT4, total thyroxine; TT3, total triiodothyronine; TSH, thyroid-stimulating hormone; FT4I, free thyroxine index; FT3I, free triiodothyronine index; rT3, reverse triiodothyronine.

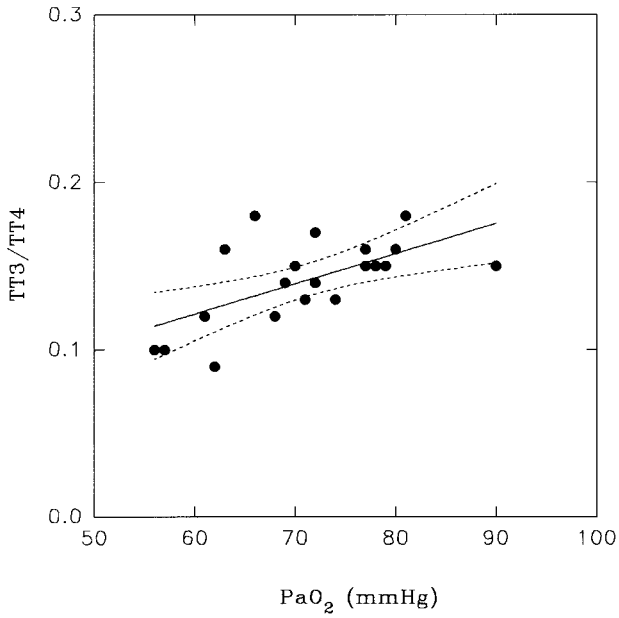

Fig 1. Correlation between TT3/TT4 ratio and PaO_2 in patients with severe COPD, ie, in those with an FEV_1 below 50% of predicted (r = .61, P = .004, n = 20). Regression line and corresponding 95% predicted confidence interval (CI) are displayed.

have been well documented in several acute and/or chronic disease states, and multiple, complex, and incompletely understood mechanisms have been implicated in their pathogenesis.[1-5] Regarding thyroid function in COPD, limited information exists, as most available studies have been performed on a small, selected series of patients, mainly on those with severe disease. Semple et al[16] measured serum TT3 and TT4 levels in 16 patients with stable COPD having a mean FEV_1 below 40% of predicted and did not find any differences among hypercapnics, normocapnics, and controls. In a subsequent study, the same investigators performed TRH stimulation tests in 8 hypoxic, stable patients (mean PaO_2, 49 mm Hg), with severe COPD (mean FEV_1 34% of predicted) and demonstrated that their resting thyroid hormone levels were normal, and that only 2 isolated patients showed a delayed TSH response; it was therefore concluded that, at most, hypoxemia causes a very minor change in the hypothalamic-pituitary-thyroid (HPT) axis at the hypothalamic-pituitary (central) level.[7] Gow et al[6] investigated thyroid function in 20 patients with exacerbations, having severe COPD (highest FEV_1 40% of predicted). There were comparable basal concentrations of thyroid hormone levels in COPD patients and controls, and in addition, only 3 elderly patients showed no TSH response to TRH. They did not demonstrate any correlation between arterial blood gas tensions and thyroid hormone levels, and it was therefore suggested that aging and illness per se might be more important than hypoxemia in determining thyroid function in COPD.[6] Similarly, Banks et al[17] studied 25 COPD patients having a spectrum in disease severity, with various degrees of hypoxemia and hypercarbia. There were no relationships between thyroid hormones and PaO_2 or $PaCO_2$, but there was an inverse correlation between serum thyroxine and the daily dose of oral pred-

nisolone; it was concluded that thyroidal dysfunction ascribed to COPD is probably related to confounding factors and not to hypoxemia or hypercapnia.[17] All of our COPD subjects, having a wide range in disease severity, had normal basal TT3, TT4, and TSH; more importantly, rT3 and IL-6, which have been shown to be elevated in patients with NTI,[3,18,19] were also within normal limits. We did not detect differences between the 2 groups of COPD patients in TSH and rT3 levels, such as those observed in the euthyroid sick syndrome (or NTI). However, it is known that, under such conditions, both TSH and rT3 may have a great variability; TSH levels are low or normal, and rT3 levels are normal or elevated.[1] Additionaly, it has been shown that rT3 is highly variable in diverse clinical situations; patients with hypothyroidism plus illness may have a normal rT3, and patients with euthyroidism may have a low rT3.[20] Consequently, our results are in agreement with previous studies regarding preserved serum thyroid hormone levels in COPD.

In other chronic conditions, such as chronic heart failure, the occurrence of thyroid dysfunction has been found to correlate with disease severity,[3] and therefore, we also aimed to ascertain this issue in the setting of COPD. For this purpose in addition to resting thyroid hormone levels, the calculated TT3 to TT4 ratio was used, as this ratio has been proven to be a useful tool in studying the peripheral conversion of thyroxine to triiodothyronine in various disease states.[21,22] Grading COPD in terms of FEV_1 as a percentage of predicted, according to international guidelines,[13] we observed a strong positive correlation between TT3/TT4 ratio and oxygenation status in patients with severe disease, but not in those with mild-to-moderate COPD. This suggests that hypoxemia may act not only at the central level of the HPT axis, as previously proposed,[7] but also, at least in the most disabled patients, by interfering with the peripheral metabolism and/or turnover of thyroidal hormones. Whether this finding represents an abnormality or it constitutes an appropriate response of the organism to severe disease is presently unknown. All patients in our study were in the overweight BMI range, but differences in mean BMI were noted between the 2 groups. Consequently, a subtle alteration in the conversion of T4 to T3, as a function of differences in the catabolic state and/or nutritional status, cannot be totally excluded.

In addition to the effect of oxygenation, we aimed to clarify also the impact of other potential contributory factors, such as aging and inhaled corticosteroids on thyroid function within COPD patients having different degrees of functional impairment. Although aging has been associated with a decline in serum thyroidal hormones, at least by some investigators, the degree to which this parameter contributes to thyroid function changes is difficult to delineate due to multiple confounding factors, such as concomitant illnesses and, in fact, this issue remains controversial.[23-25] Our results do not support the hypothesis that in COPD increasing age influences thyroid hormone measurements or metabolism, because there were no significant correlations between any thyroid hormones and age neither in mild-to-moderate nor in severe disease.

Oral corticosteroids may affect thyroid function tests by suppressing TSH synthesis and secretion causing a state of central hypothyroidism.[26,27] They also modulate peripheral hormone metabolism by diverting the deiodination of T4 from the activating (T4 leading to T3) to the inactivating (T4 leading to rT3) pathway.[28] All patients in our study were in stable condition and, therefore, none of them was receiving oral steroids, but a significant percentage of them were on inhaled steroids. High-dose inhaled corticosteroids (above 1.5 mg/day) have been associated with marked systemic adverse effects, especially with adrenal suppression.[29] Thus, although studies on the impact of inhaled steroids on the hypothalamic-pituitary-adrenal axis have been presented, few studies have addressed the issue of the effect of inhaled steroids on the HPT axis. Theoretically, high doses of inhaled steroids could alter thyroid hormone levels in a similar way to that of oral steroids. Nevertheless, our study did not show any relationship between inhaled steroids and thyroid function tests either in mild-to-moderate or in severe COPD, and this is probably explicable by the fact that the mean dose of inhaled steroids in our patients was only about 900 μg/day.

In conclusion, we have demonstrated that in stable COPD baseline thyroid hormones are within normal limits; however, in those with severe disease, hypoxemia can produce abnormalities in thyroid function, which are located not only in the hypothalamic-pituitary (central) level as previously suggested,[7] but also, at least in part, in the periphery. The clinical significance of this finding remains to be clarified.

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