



doi • 10.5578/tt.68257  
Tuberk Toraks 2019;67(2):131-135  
Geliş Tarihi/Received: 23.04.2019 • Kabul Ediliş Tarihi/Accepted: 05.05.2019

DERLEME  
REVIEW

# An underestimated comorbidity of COPD: Thyroid dysfunction

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*Cite this article as: Akpınar EE. An underestimated comorbidity of COPD: Thyroid dysfunction. Tuberk Toraks 2019;67(2):131-5.*

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## SUMMARY

### An underestimated comorbidity of COPD: Thyroid dysfunction

Chronic obstructive pulmonary disease (COPD) has many systemic effects influencing morbidity and mortality of the disease. Thyroid diseases which are more common in COPD patients than who do not have COPD are underestimated despite important clinical consequences. Similar to general population, thyroid dysfunctions are more common in females than males among COPD patients. Both hypothyroidism and hyperthyroidism may be associated to COPD. As well as systemic inflammation hypoxia, age, glucocorticoid use and smoking are some of the effective factors on developing thyroid dysfunction in COPD patients. In this article thyroid dysfunctions that are underrecognized comorbidities of COPD patients, their mechanisms of action and clinical outcomes were reviewed.

**Key words:** Chronic obstructive pulmonary disease; comorbidity; thyroid gland

## ÖZET

### KOAH'ta göz ardı edilen bir komorbidite: Tiroid disfonksiyonu

Kronik obstrüktif akciğer hastalığı (KOAH)'nın morbidite ve mortalitesini etkileyen birçok sistemik etkisi vardır. KOAH'lı hastalarda KOAH olmayanlara göre daha sık görülen tiroid hastalıkları önemli klinik sonuçlarına rağmen yeterince önemsenmemektedir. Genel popülasyona benzer bir şekilde tiroid disfonksiyonları kadın KOAH'lılarda erkeklerden daha sık görülmektedir. Hem hipotiroidizm hem de hipertiroidizm KOAH'a eşlik edebilmektedir. KOAH'lı hastalarda sistemik inflamasyonun yanı sıra hipoksi, yaş, glukokortikoid kullanımı ve sigara içilmesi tiroid disfonksiyonu gelişiminde etkili olan bazı faktörlerdir. Bu derlemede KOAH'lı hastalarda az bilinen bir komorbidite olan tiroid disfonksiyonları, gelişim mekanizmaları ve klinik sonuçları gözden geçirilmiştir.

**Anahtar kelimeler:** Kronik obstrüktif akciğer hastalığı; komorbidite; tiroid bezi

**INTRODUCTION**

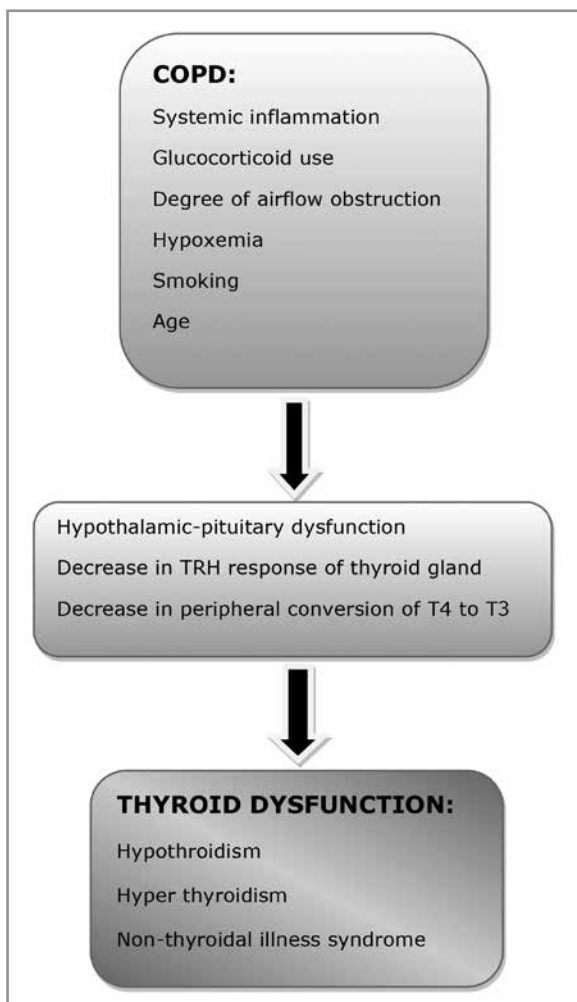
Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. The disease courses with chronic airway inflammation. The inflammation not only affect the airways but also has systemic effects that are main causes of comorbidities (1). Some comorbidities such as coronary artery disease, metabolic syndrome are well-recognized in COPD patients. But, thyroid diseases which are more common in COPD patients than who do not have COPD are underestimated despite important clinical consequences (2). Similar to general population, thyroid dysfunctions are more common in females than males among COPD patients. In a large COPD cohort from Spain, prevalence of thyroid diseases was reported as 14.2% and it was found higher in females than males (24.6 vs 10.9%) (3).

Thyroid hormones have an important role in regulation of metabolism. They may change the respiratory drive as a result of their effects on metabolic rate and transcription of some genes related to myofibres (4). Systemic inflammation may express the link between COPD and thyroid diseases. Supporting this postulate, Karadag et al. found a positive correlation between IL-6 which is a systemic inflammation marker and total triiodotironine (TT3) and TT3/TT4 (total thyroxine) in patients with stable COPD (5). Smoking itself increase systemic inflammation independently from associating COPD and may affect thyroid functions. Both of the hypothyroidism and hyperthyroidism may associate with COPD (4). The aim of the article is to review thyroid dysfunctions in patients with COPD and to emphasize clinical consequences of these comorbidities which are usually underestimated. The relationship between COPD and thyroid gland dysfunction was summarized on Figure 1.

**Hypothyroidism and COPD**

Hypothyroidism is more frequent than hyperthyroidism among COPD patients. Patients with COPD can present with increased systemic levels of inflammatory cytokines such as IL-6, IL-1 and TNF- $\alpha$  that can inhibit the synthesis or secretion of thyroid stimulating hormone (TSH), T3 and thyroid hormone-binding proteins, and can decrease the conversion of T4 to T3 (6). In addition to systemic inflammation severity of airflow obstruction, hypoxemia and corticosteroid use in COPD patients are predisposing factors in development of hypothyroidism. Moreover, aging also was suggested as a determinant factor on hypothalamic-pituitary dysfunction in elderly patients with COPD (7). Glucocorticoids which are frequently used in COPD treatment may cause decrease in serum TSH and in conversion of T4 to T3. They also may lead to redistribution of thyroid hormones in body fluids (6).

Previous studies showed that hypothyroidism was more common than hyperthyroidism in COPD patients and its frequency showed positive correlation with the stage of COPD (8,9). Hypothyroidism may cause respiratory muscle dysfunction in patients with or without COPD. The decrease in neuromuscular transmission and expression of some proteins related to myofibers are main causes of the dysfunction of respiratory muscles. Phrenic nerve neuropathy also may contribute to weakness of respiratory muscles (6). Ulasli et al. found that maximum expiratory pressure (MEP) levels were significantly lower in COPD patients



**Figure 1.** The relationship between chronic obstructive pulmonary disease and thyroid gland dysfunction.

with hypothyroidism than in those without it (10). Moreover, Terzano et al. showed that COPD patients with hypothyroidism had lower PaO<sub>2</sub> and a tendency to increase in PCO<sub>2</sub> levels. They also found that levels of maximum inspiratory pressure (MIP) and MEP were lower in this group of COPD patients (10,11). Dimopoulou et al. found a positive correlation between TT3/TT4 and PaO<sub>2</sub> in COPD patients who had FEV<sub>1</sub> < 50% (12). Alveolar hypoventilation secondary to respiratory muscle dysfunction and decreased ventilatory drive may enhance hypoxemia and hypercapnia in COPD patients (6).

The exacerbation frequency was found to be higher in COPD patients associated with hypothyroidism than those did not (8,10). The frequency of COPD exacerbation was positively correlated with TSH levels and TSH value was found as a significant determinant of exacerbation frequency (10). Furthermore, Bacakoglu et al. demonstrated that low fT3 and fT4 levels increase the rates of invasive mechanical ventilation and mortality in patients with respiratory failure (12,13). Although COPD patients with hypothyroidism have exercise intolerance and decreased maximal oxygen uptake, the study of Ulasli et al. concluded that hypothyroidism was not a factor affecting quality of life in COPD patients (5,10). Further studies are needed to determine effects of hypothyroidism on COPD exacerbation and also to clarify its effects on outcomes of respiratory failure and quality of life in COPD patients.

Obstructive sleep disorders are commonly seen in hypothyroid patients with or without COPD. Obesity,

mucoprotein deposition and myopathy and, decreased ventilatory drive are possible causes of sleep disorders in hypothyroid patients (4).

The treatment of hypothyroidism associated with COPD does not differ from the treatment of patients without it (6). Although some negative effects of hypothyroidism may be reversed with treatment, the effect of treatment on lung functions and prognosis is not well known and should be clarified with future studies.

Clinical consequences and their mechanisms in COPD patients with hypothyroidism were shown on Table 1.

### Hyperthyroidism and COPD

Hyperthyroidism is less frequently seen than hypothyroidism in COPD patients. Muscle weakness due to loss of muscle mass and strength as a result of increased catabolism can be seen in COPD patients with hyperthyroidism. COPD patients who have cachexia should be investigated whether they have concomitant hyperthyroidism. Muscle wasting that is already present in COPD patients may be aggravated by hyperthyroidism (4). Siafakas et al. reported that inspiratory and expiratory muscle weakness (decrease in FEV<sub>1</sub>, FVC, VC, MEP and MIP) was proportional to the level of hyperthyroidism and reversible with treatment in thyrotoxic patients (14).

The increase in TT3/TT4 and fT3 in COPD patients were previously reported (10,15). El-Yazed et al. demonstrated that the increase in fT3 showed negative correlation with PaO<sub>2</sub> and positive correlation with

**Table 1.** Clinical consequences and their mechanisms in chronic obstructive pulmonary disease patients with hypothyroidism

Clinical consequence	Mechanism
Decrease in MEP and MIP	Respiratory muscle dysfunction: Decrease in neuromuscular transmission Decrease in myofiber protein expression Phrenic nerve neuropathy
Alveolar hypoventilation	Decrease in ventilatory drive Respiratory muscle weakness Pleural effusion
Obstructive sleep disorders	Obesity Mucoprotein deposition Myopathy Decrease in ventilatory drive
Increase in exacerbation frequency	Respiratory muscle dysfunction Decrease in ventilatory drive Susceptibility to respiratory infections

MEP: Maximum expiratory pressure, MIP: Maximum inspiratory pressure.

PaCO<sub>2</sub> and also proportional to the severity of COPD (15). The excess T3 level causes proteolysis which can be augmented by glucocorticoid treatment in respiratory muscles including diaphragm. In addition to increase in T3 levels, loss of TSH response to thyroid releasing hormone (TRH) was another disturbance that was shown in elderly severe COPD patients (7).

The risk of respiratory failure is increased in patients with hyperthyroidism as a result of respiratory muscle weakness, decreased lung compliance and increased sensitivity of peripheral and central chemoreceptor sensitivity (6). Treatment of COPD patients with hyperthyroidism is same with hyperthyroid patients without COPD.

### **Non-Thyroidal Illness Syndrome in COPD**

Non-thyroidal illness syndrome (NTIS) is characterized by a decrease in peripheral conversion of T4 to T3 because of a systemic disease (16). It is the most frequent type of thyroid function impairment among COPD patients. The estimated prevalence of NTIS is 14-20% in patients with stable COPD and 70% in exacerbation period. The levels of T3 which is biologically active hormone decreased, T4 levels are normal or decreased in NTIS and they usually have a normal level of TSH (6).

Karadag et al. investigated thyroid hormone levels in COPD patients both in stable phase and exacerbation period and in control group. They found that fT3 levels and TT3/TT4 ratio were lower in the COPD group than in controls. Additionally, they demonstrated that alterations in thyroid hormone levels were more prominent in exacerbation period and they turned to normal levels subsequent to recovery of exacerbation. They also reported that stable COPD patients had significant changes in thyroid hormones, which were correlated with severity of disease and hypoxemia (5). The authors warned about that the assessment of thyroid function during exacerbation period may be misleading and thyroid function abnormalities in stable phase related to non-thyroidal illness may mimic true thyroid disease (5).

NTIS may cause worse outcomes in clinical course of COPD patients. Yasar et al. examined the relationship between NTIS and prolonged weaning in COPD patients admitted to the ICU. They reported that NTIS had predictive role for prolonged weaning in COPD patients who undergo invasive mechanical ventilation (17).

Mancini et al. investigated the relationship between thyroid hormones and antioxidant systems, the lipophilic Coenzyme Q10 and total antioxidant capacity in COPD patients. They found lower antioxidant capacity in COPD patients with normal fT3 levels, compared to healthy control group and further significant reduction in COPD patients with low level of fT3. They suggested that oxidative stress increases in COPD patients with low level of fT3 and these patients may benefit from thyroid replacement therapy (18). It is not yet obvious whether supplemental therapy is useful or not in all COPD patients with NTIS. Future studies are necessary to clarify effects of hormonal therapy in these patients.

### **CONCLUSION**

Despite important clinical consequences that may negatively affect course and prognosis of the disease, thyroid dysfunctions are frequently underrecognized comorbidities of COPD. Hypothyroidism is more prevalent than hyperthyroidism and NTIS is the most frequently seen thyroid dysfunction in COPD patients. Thyroid dysfunctions may cause worse clinical outcomes in COPD patients such as increase in exacerbation frequency and prolonged intubation. The evaluation of COPD patients for thyroid dysfunctions may be useful because hormone replacement therapy can reverse most of the negative effects of this comorbidity both in hypothyroid and hyperthyroid patients. But, its effect is not clear in COPD patients with NTIS. Future studies are needed to determine which COPD patients should be evaluated for thyroid dysfunctions and which NTIS patients will benefit from supplemental therapy. Population-based studies are necessary to find out exact prevalence of thyroid dysfunction in COPD patients.

### **CONFLICT of INTEREST**

The authors reported no conflict of interest related to this article.

### **AUTHORSHIP CONTRIBUTIONS**

Concept/Design: EEA

Analysis/Interpretation: EEA

Data Acquisition: EEA

Writing: EEA

Critical Revision: EEA

Final Approval: EEA

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