

Joanna Miłkowska-Dymanowska^{1,2}, Adam J. Białas^{1,2}, Paulina Laskowska³, Paweł Górski^{1,2},
Wojciech J. Piotrowski^{1,2}

¹Department of Pneumology and Allergy, Healthy Ageing Research Centre Medical University of Lodz, Poland

²Healthy Aging Research Centre (HARC), Medical University of Lodz, Poland

³Student, Faculty of Medicine, Medical University of Lodz, Poland

Thyroid gland in chronic obstructive pulmonary disease

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Abstract

The risk of chronic obstructive pulmonary disease (COPD), as well as thyroid diseases increases with age. COPD is a common systemic disease associated with chronic inflammation. Many endocrinological disorders, including thyroid gland diseases are related to systemic inflammation. Epidemiological studies suggest that patients with COPD are at higher risk of thyroid disorders. These associations are not well-studied and thyroid gland diseases are not included on the broadly acknowledged list of COPD comorbidities. They may seriously handicap quality of life of COPD patients. Unfortunately, the diagnosis may be difficult, as many signs are masked by the symptoms of the index disease. The comprehension of the correlation between thyroid gland disorders and COPD may contribute to better care of patients. In this review, we attempt to revise available literature describing existing links between COPD and thyroid diseases.

Key words: COPD, comorbidity, thyroid gland, hypothyroidism, hyperthyroidism

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide [1]. The risk increases suddenly with age, and the peak incidence falls when patients are over 60 [1]. It has been acknowledged that chronic inflammation occurring in COPD is systemic in nature, but it occurs primarily in the lung, from where inflammatory cytokines “spill over” and inflammation spreads to other organs of the body [1–3]. Systemic inflammation may be driven by the main risk factor — cigarette smoking, and it persists after smoking cessation [1, 3, 4]. The inflammation has an impact on other systems, for example: cardiovascular, skeletal muscles, skeleton, brain etc. [3–5]. According to GOLD (Global Initiative for Obstructive Lung Disease), many comorbidities like coronary artery disease, diabetes and metabolic syndrome, de-

pression, cachexia, osteoporosis are undoubtedly associated with COPD by their frequent co-occurrence [1]. The link between other chronic diseases and COPD may not be so obvious, but some data suggest many underrecognized associations [5]. COPD interferes with endocrinological homeostasis not only by means of systemic inflammation [6]. Other factors like neurohormones, blood gas abnormalities, glucocorticoid administration also disturb hormonal balance [6]. On the other hand, hormones may affect regulation of breathing [7]. Some hormones act on the level of the central nervous system, some have an impact on peripheral chemoreceptors, others may contribute to this process by influencing the metabolism rate, and others exert their effect directly on receptors in the respiratory tract [7]. Drugs frequently used by COPD patients to treat comorbidities, such as amiodarone [8], lithium carbonate [9] or potassium iodine [10] may lead to hypothyroidism.

Address for correspondence: Wojciech J. Piotrowski, Klinika Pneumonologii i Alergologii, I Katedra Chorób Wewnętrznych UM w Łodzi, ul. Kopcińskiego 22, 90–153 Łódź

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On the other hand, there are known cases of thyrotoxicosis induced by iodinated glycerol [11], amiodarone [12] or lithium salts [9].

There is a growing evidence that thyroid gland function may be disturbed in COPD patients [2, 5, 13–16]. Some studies show that thyroid diseases are more frequent among patients with COPD. In a big population-based study performed in the city of Madrid, Spain, it was shown that the prevalence of a thyroid disease was higher in COPD patients (14.21%) than the expected standardized prevalence of chronic diseases (11.06%) [5]. The general occurrence of thyroid disorders is estimated at 14–20% among stable COPD patients [5, 17] and at 70% during an exacerbation [17]. The thyroid diseases occur more frequently among women than men with COPD [5], the same as in the general population [18].

The aim of this review is to discuss the available data on the coexistence of thyroid gland disorders in COPD.

Search methodology

The initial search was conducted using PubMed with the subject headings “pulmonary disease, chronic obstructive pulmonary disease” and “endocrinological disorders” or “endocrinology”. All abstracts were assessed for relevance, and articles of the relevant studies were retrieved. Subsequent searches utilized the following combinations of subject headings on PubMed: “COPD & thyroid hormones” or “COPD & thyroid disorders” or “COPD & hypothyroidism” or “COPD & hyperthyroidism” or “COPD & non-thyroidal illness syndrome”. For relevant titles, the abstracts were reviewed and, if still relevant, the article in full version was retrieved. References within the selected articles were also reviewed in terms of their relevance. Table 1 shows a number of hits and final selection from each thematic area. According to PRISMA guidelines, this review should be classified as a narrative systematic review [19].

Chronic inflammation as a possible link between COPD and thyroid gland diseases

Chronic inflammation in COPD is associated with production of interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , IL-8, IL-6, and fibrinogen by alveolar macrophages and neutrophils [20]. In humans, intravenous administration of recombinant IL-6 resulted in acute reduction of triiodothyronine (T3) and thyroid stimulating hormone (TSH) levels [21]. Karadag *et al.* assessed thyroid hormones and both serum IL-6 and TNF- α

during exacerbation period, recovery and stable phase of COPD. As expected, cytokine levels were higher in patients with COPD (both stable and exacerbated), compared to age and sex — adjusted control group [17]. The authors found a positive correlation between IL-6 and total triiodothyronine (TT3) and TT3/TT4 in stable patients [17].

Tobacco smoke contains considerable amounts of free radicals that may damage the structure of the respiratory tract and promote inflammation [1, 22]. Cigarette smoke attracts activated inflammatory cells to the lungs - another source of free radicals and oxidants contributing to sustained inflammation [23]. Also the endocrine system is not inert to the components of cigarette smoke [24–26]. Higher levels of serum total triiodothyronine (TT3) were found in young healthy smokers comparing to non-smoking control subjects [25], what may suggest that smoking acts independently of coexistent diagnosis of COPD. Figure 1 presents possible links between tobacco smoking, chronic inflammation, systemic nature of COPD, and thyroid dysfunction.

Hypothyroidism

The prevalence of hypothyroidism in the general population is 0.9% among men and 4.8% among women [27]. Its frequency increases with age [18]. Some studies have shown the relationship between thyroid hormone levels and blood gas parameters [2]. Terzano *et al.* [2] described lower blood oxygen pressure (pO₂) in patients with overt hypothyroidism, compared to other groups consisting of patients with subclinical hypothyroidism, normal subjects and patients with hyperthyroidism. Moreover, in the same research, the authors observed significant increase of the blood carbon dioxide pressure (pCO₂) levels in patients with hypothyroidism, although a correlation between TSH and pCO₂ was not present [2].

Dimopoulou *et al.* reported strong positive correlation between serum total triiodothyronine/total thyroxine (TT3/TT4) ratio and arterial oxygen pressure (PaO₂), but only in COPD patients with FEV₁ <50% predicted value, and not in those above this threshold [28]. This observation suggests the relationship between low conversion rate of T4 to T3 in peripheral tissues and hypoxemia in most severe COPD patients [29]. In another study, it was demonstrated that obstruction severity is associated with reduced basal and stimulated thyroid stimulating hormone (TSH) [30]. However, the exact mechanism of the above connection is not known.

Muscle weakness is one of the symptoms of hypothyroidism [2, 31]. The deterioration of main respiratory muscle function [32] aggravates already weakened ventilation in patients with COPD [2]. Some adapting mechanisms in COPD

patients have been described, like shortening of the length of sarcomeres and an increase in the concentration of mitochondria [32]. The muscle weakness may manifest in worse spirometry results [2]. In hypothyroidism mean inspiratory pressure (MIP) and mean expiratory pressure (MEP) are decreased [2, 31], supposedly due to decreased respiratory muscle strength [33]. The association of free T3 (fT3) level with arterial blood gases and pulmonary function parameters (vital capacity [VC] or forced vital capacity [FVC], FEV₁, peak expiratory flow [PEF]) has been demonstrated [14]. Another study also confirmed lower values of MEP in COPD patients with hypothyroidism than in those without this condition [31]. The authors observed significantly lower values of FVC, FEV₁/FVC, forced expiratory flow at 25 and 75% (FEF_{25-75%}) in this group of patients [31]. Others reported on correlation between MEP and MIP values and thyroid function [2]. Interestingly, there is also a positive correlation between TSH values and acute exacerbations frequency [31]. Among the patients with hypothyroidism, the exacerbations occurred more frequently than in patients without hypothyroidism, and TSH value turned out to be the only significant determinant of exacerbation frequency [31]. Further studies are needed to verify if impaired thyroid function really increases the risk of COPD exacerbation and if proper hormonal treatment would impact the clinical outcome. Authors of other studies reported on lower spirometry parameters in patients without clinically diagnosed hypothyroidism, but with low values of thyroid hormones, that still remained within normal limits [14]. It is of note that the muscle weakness, caused by hypothyroidism, is reversible after treatment [33].

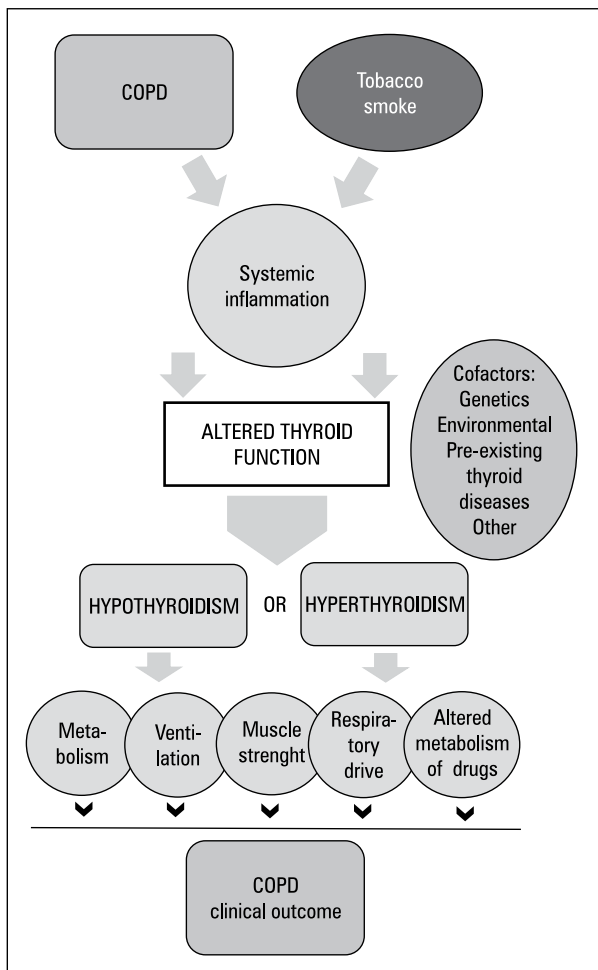


Figure 1. Possible links between chronic obstructive pulmonary disease, cigarette smoking and thyroid gland disorders

Thyroid dysfunction, defined by the use of thyroid function tests (TFT), was demonstrated in

Table 1. The process of Pubmed search in selected areas

Search area	Combination of PubMed terms "COPD" and:	PubMed search	Abstract selection	The most relevant for the topic
Endocrinological Disorders	Endocrinological Disorders	14	12	3
	Endocrinology	95	34	10
Thyroid	Thyroid	146	24	5
	Thyroid disorders	156	50	21
	Hypothyroidism	81	27	18
	Hiperthyroidism	43	14	5
	Non-thyroidal illness syndrome	2	2	2

more than half of COPD patients with respiratory failure (52.3%) and in slightly lower percentage of patients without this condition (44.4%) [34], however, the difference between the groups was not statistically significant. Moreover, patients with both low levels of fT3 and free T4 (fT4) needed invasive mechanical ventilation more often than those from the group with normal TFT scores [34]. The authors also observed the higher rate of in-hospital mortality among patients with low levels of either fT3 or fT4 [34]. Significant difference of TSH level between groups of patients with COPD exacerbation and healthy subjects was demonstrated [34]. Lower fT3 in the course of COPD exacerbation was also confirmed by other authors [16]. The authors also found that fT3 negatively correlated with bicarbonate levels and fT4, also negatively, with hemoglobin [16].

Hyperthyroidism

Hyperthyroidism occurs in the general population with a frequency of 2.5% in women and 0.6% in men [27]. One study assessed a prevalence of subclinical hyperthyroidism among a group of 34 men with COPD, and estimated the rate at 20.6%, however, the examined group was too small to extrapolate the results to entire population of COPD patients [24]. Further studies to verify these results are needed.

The hyperthyroidism itself may influence pattern of breathing, probably due to the action of thyroid hormones on central (increased hypoxic drive) and peripheral (hypercapnic drive) regulatory mechanisms. Dyspnea and hyperventilation are frequent in patients with hyperthyroidism, and may lead to relatively higher levels of pO₂ and lower levels of pCO₂ [2, 7]. In patients with COPD and hyperthyroidism, muscle weakness may also appear, and may result from increased catabolism [33, 35]. The loss of muscle mass and muscle strength in patients with thyrotoxicosis has been confirmed [36]. Similarly to hypothyroidism, loss of muscle mass may be responsible for decreased lung function. Siafacas *et al.* [35] confirmed decreased FEV₁, FVC, VC, MEP and MIP in hyperthyroid patients, compared to euthyroid subjects (COPD patients were excluded from the study). All these parameters improved significantly after treatment, with the exception of FEV₁/FVC ratio [35]. MEP and MIP were measured to define global respiratory muscle strength [35]. Both of the above values were reduced, compared to results of the control group, and they also increased after treatment of hyperthyroidism [35]. Similar results

were obtained in another study, where MEP and MIP also increased significantly after treatment of hyperthyroidism [37]. A significant correlation was reported between T3, T4 levels and MEP and MIP [35]. There was no association between maximal expiratory and inspiratory pressures and TSH [35]. The muscles wasting phenomenon may also result from malnutrition, which is common in patients with COPD [38, 39]. Regardless of the reason, muscle weakness may be a cause of respiratory failure, therefore it may be of special importance to diagnose and treat hyperthyroidism as a reversible factor in respiratory failure [40].

Uzun *et al.* have demonstrated higher proportion of patients with low TSH in severe COPD patients compared to healthy control group, although the mean values of TSH, fT3 and fT4 were not significantly different between groups [15]. Similarly, Dimopoulou *et al.* did not find significant difference in mean levels of TSH, fT3 and fT4 between mild to moderate COPD patients and control group, however the authors found strong negative correlation between TT3/TT4 ratio and pO₂ in the sub-group of the most severe COPD patients [28]. This finding was confirmed by Hussein *et al.* [41], who found higher levels of fT3 in COPD group and significant negative correlations between fT3 levels and both PaO₂ and saturation of hemoglobin with oxygen (SatO₂), and pulmonary function tests results of COPD patients. Severity of COPD increased significantly with growing fT3. The authors suggested that fT3 may be a marker of systemic impact of COPD [41]. The authors also reported on the positive correlation between fT3 and PaCO₂ [41], thus confirming earlier results of another group of authors [14]. This observation is somewhat unexpected, as the tendency to hyperventilation and hypocapnia was rather reported in non-COPD thyrotoxic patients [2, 7]. This may reflect the alveolar hypoventilation present in COPD patients, which enables “washing out” the excess of CO₂ from the alveoli. In contrast to Hussein’s results, Gow *et al.* [42] did not find significant differences in thyroid hormones levels between COPD and non-COPD elderly patients. In this study, delayed and reduced TSH responses to thyrotropin releasing hormone (TRH) also occurred in both groups, indicating that the changes in the hypothalamic-pituitary-thyroid axis were not specific to hypoxic patients. Reduced responses have been described as an age related effect, particularly in men, whereas delayed responses were thought to indicate hypothalamic damage. Absence of TSH response to TRH occurred only in patients with COPD but

this has been described in elderly patients with various acute illnesses. The severe illness and possible malnourishment of COPD patients are likely to have had an additional suppressive effect on the TSH response to TRH [42].

Hypermetabolism in COPD

Hypermetabolism is common among patients with COPD [43]. Coenzyme Q10 [CoQ10] is used to characterize the metabolic status in patients suffering from thyroid disorders [44]. It was shown that CoQ10 and thyroid hormones are inversely correlated [44]. The level of CoQ10 in hypothyroidism (even in subclinical cases) is elevated [36], while CoQ10 level in patients with hyperthyroidism is reduced [44]. In the cited study, significantly higher values of CoQ10 in a group of COPD patients with low fT3 levels were observed, compared to COPD patients with normal fT3 levels [44]. Similar results were noted, comparing these two groups in respect to CoQ10/cholesterol ratio. Again, the COPD group with low fT3 showed higher levels of this ratio than COPD group with normal fT3 [44].

The weight control in patients with COPD is an important issue. Hypermetabolism in hyperthyroidism and hypometabolism in hypothyroidism may complicate the treatment of patients with chronic diseases. Therefore, further researches on the utility of the above index are necessary because they can provide information about the level of metabolism. Together with incorrect dietary intake, it may lead to weight loss. Interestingly, the occurrence of thyroid dysfunction has not been evaluated for its influence on cachexia in patients with COPD so far [43].

Non-thyroidal illness syndrome

Non-thyroidal illness syndrome (NTIS) may be defined as reduced conversion of T4 to T3 in different acute and chronic systemic disorders. NTIS occurs more frequently than hypothyroidism and subclinical hypothyroidism [16]. This clinical entity is characterized by a decreased TT3 and fT3, normal or decreased TT4 and fT4, and unchanged TSH levels [17]. The mechanisms leading to NTIS are largely unknown and further studies in this field are required [16]. Karadag *et al.* [17] evaluated 103 moderate-to-severe COPD patients and 30 controls with normal pulmonary function. The COPD group was further divided into patients with stable disease and with acute exacerbation. The study showed that TT3 and

fT3 levels and TT3/TT4 ratio were lower in the COPD group than in controls, and the difference was more significant for fT3. Besides, TSH, TT3, fT3 levels and TT3/TT4 ratio were lower in the exacerbation group in comparison with the stable COPD group. In addition, serum TT3 and TT3/TT4 ratio were lower in severe, compared to moderate COPD. Moreover, in patients with exacerbation, TSH, TT3, fT3 levels and TT3/TT4 ratio increased in follow-up measurements on the day of discharge from hospital and one month later. The hormonal changes during follow-up after COPD exacerbation followed normalization of PaO₂ and PaCO₂ during recovery. The increase of TSH levels following improvement of hypoxia and stabilization of clinical condition denotes delayed pituitary response to TRH, which was earlier impaired by hypoxia [17]. On the contrary, Gow *et al.* [42] did not find any correlation between arterial blood gases and thyroid hormones, and therefore suggested that aging and illness *per se* might be more important factors leading to thyroid dysfunction than hypoxemia. Serum TT3, fT3 and TT3/TT4, which decrease with age and in COPD exacerbations as shown in the cited study, indicate decreased metabolic clearance of T4 and decreased peripheral conversion to T3. This inverse correlation suggests that aging may also play a role in thyroid dysfunction in addition to hypoxemia [16]. According to foregoing findings, thyroid disease should not be recognized during COPD exacerbation because of alternations in thyroid hormones related to severe clinical condition and not to true thyroid disease [17]. In another study, it was shown, that NTIS may be regarded as independent predictor of prolonged weaning in intubated COPD patients [45]. Importantly, prolonged weaning is associated with increased mortality and morbidity in the intensive care unit [45]. Presumably, NTIS (especially low fT3) may reflect severity of inflammation, hypoxia or other pathological processes associated with COPD exacerbation [45]. Furthermore, the authors proposed to add baseline thyroid function tests to the predictive capacity of the APACHE II score [45]. The authors also reported on successful weaning from mechanical ventilation (MV) after proper hormonal supplementation in patients with newly diagnosed hypothyroidism [45]. Although the authors noticed that further studies are necessary to assess the significance of thyroid hormones supplementation in patients with NTIS [45].

It should be remembered that various factors can affect thyroid function by stimulating or suppressing it [17, 45]. More frequent occurrence of

pulmonary infections among patients with NTIS has been demonstrated [45]. Some cytokines and immune system cells restrain thyroid gland activity [45]. Therefore, treatment of pulmonary infections or any infection, becomes an important aim to reach.

Conclusions

The signs or symptoms of thyroid disorders may be non-specific, especially among the elderly, therefore the differential diagnosis between symptoms of COPD and symptoms related to thyroid disease can cause difficulties. Many data show higher risk of thyroid hormones alterations (both hyper or hypothyroidism) in COPD patients. Both hyperthyroidism and hypothyroidism may influence respiration by different mechanisms, even in subjects with intact respiratory system. Therefore it is hard to distinguish whether hormonal changes are the reason or a consequence of different respiratory signs and symptoms. In some instances the correction of hormonal alternations may improve the quality of life of COPD patients and other disease outcomes. The comprehension of an association between COPD, thyroid gland function and thyroid disorders may provide important information about the systemic nature of COPD.

Conflict of interest

The authors declare no conflict of interest.

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