Hypothyroidism and chronic obstructive pulmonary disease

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. 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 in COPD patients. 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. Keywords: hypothyroidism; chronic obstructive pulmonary disease; comorbidity; thyroid gland

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 [2].

Systemic inflammation may be driven by the main risk factor — cigarette smoking, and it persists after smoking cessation [3]. The inflammation has an impact on other systems, for example: cardiovascular, skeletal muscles, skeleton, brain etc. [4]. According to GOLD (Global Initiative for Obstructive Lung Disease), many comorbidities like coronary artery disease, diabetes and metabolic syndrome, depression, 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.

There is a growing evidence that thyroid gland function may be disturbed in COPD patients [2, 7, 11]. 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 (14.2 %) than the expected standardized prevalence of chronic diseases (11.16 %) [6]. The general occurrence of thyroid disorders is estimated at 14–20 % among stable COPD patients and at 70 % during an exacerbation [12].

The thyroid diseases occur more frequently among women than men with COPD [6], the same as in the general population [13].

The purpose of this review is to discuss the available data on the coexistence of hypothyroidism and COPD.

Materials and methods

The initial search was conducted using PubMed with the subject headings “pulmonary disease, chronic obstructive pulmonary disease” and “hypothyroidism”. 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 & hyperthyroidism” or “COPD & non-thyroidal illness syndrome”.

Chronic inflammation as a possible link between COPD and hypothyroidism

Chronic inflammation in COPD is associated with production of interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-8, IL-6, and fibrinogen by alveolar macrophages and neutrophils [14]. In humans, intravenous administration of recombinant IL-6 resulted in acute reduction of triiodothyronine (T3) and thyroid stimulating hormone (TSH) levels [15]. Tobacco smoke contains considerable amounts of free radicals that may damage the structure of the respiratory tract and promote inflammation [1, 16]. Cigarette smoke attracts activated inflammatory cells to the lungs — another source of free radicals and oxidants contributing to sustained inflammation [17]. Also the endocrine system is not inert to the components of cigarette smoke. Higher levels of serum total triiodothyronine (T3) were found in young healthy smokers comparing to non-smoking control subjects [16], what may suggest that smoking acts independently of coexistent diagnosis of COPD.

Hypothyroidism

The prevalence of hypothyroidism in the general population is 0.9 % among men and 4.8 % among women [19]. Its frequency increases with age [20]. Some studies have shown the relationship between thyroid hormone levels and blood gas parameters [2]. C. 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 (fT3/fT4) ratio and arterial oxygen pressure (PaO2), but only in COPD patients with FEV1 < 50 % predicted value, and not in those above this threshold [21]. This observation suggests the relationship between low conversion rate of T3 to T4 in peripheral tissues and hypoxemia in most severe COPD patients [22]. In another study, it was demonstrated that obstruction severity is associated with reduced basal and stimulated TSH [23]. However, the exact mechanism of the above connection is not known.

Muscle weakness is one of the symptoms of hypothyroidism [24, 25]. The deterioration of main respiratory muscle function [26] 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 [26]. The muscle weakness may manifest in worse spirometry results [2]. In hypothyroidism mean inspiratory pressure (MIP) and mean expiratory pressure (MEP) are decreased [2, 27], supposedly due to decreased respiratory muscle strength [28].

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 [29]. Another study also confirmed lower values of MEP in COPD patients with hypothyroidism than in those without this condition [30]. The authors observed significantly lower values of FVC, FEV1/FVC, forced expiratory flow at 25 and 75 % (FEF25–75 %) 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 [29]. It is of note that the muscle weakness, caused by hypothyroidism, is reversible after treatment [32]. Thyroid dysfunction, defined by the use of thyroid function tests (TFT), was demonstrated in more than half of COPD patients with respiratory failure (52.3 %) and in slightly lower percentage of patients without this condition (44.4 %) [33], 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 [29]. The authors also found that fT3 negatively correlated with bicarbonate levels and rT3, also negatively, with hemoglobin [35].
Non-thyroidal illness syndrome

Non-thyroidal illness syndrome (NTIS) may be defined as reduced conversion of $T_4$ to $T_3$ in different acute and chronic systemic disorders. NTIS occurs more frequently than hypothyroidism and subclinical hypothyroidism [36]. This clinical entity is characterized by a decreased $tT_4$, and $fT_3$, normal or decreased $tT_3$ and $fT_3$, and unchanged TSH levels [37]. The mechanisms leading to NTIS are largely unknown and further studies in this field are required [38].

The hormonal changes during follow-up after COPD exacerbation followed normalization of PaO$_2$ and PaCO$_2$ 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 [39]. Serum $tT_3$, $fT_3$, and $fT_4$/$tT_4$, which decrease with age and in COPD exacerbations as shown in the cited study, indicate decreased metabolic clearance of $T_3$ and decreased peripheral conversion to $T_3$. This inverse correlation suggests that aging may also play a role in thyroid dysfunction in addition to hypoxemia [40]. 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 [41]. In another study, it was shown, that NTIS may be regarded as independent predictor of prolonged weaning in intubated COPD patients [42]. Importantly, prolonged weaning is associated with increased mortality and morbidity in the intensive care unit [43].

Presumably, NTIS (especially low $fT_3$) may reflect severity of inflammation, hypoxia or other pathological processes associated with COPD exacerbation [44]. 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. More frequent occurrence of pulmonary infections among patients with NTIS has been demonstrated [46]. Some cytokines and immune system cells restrain thyroid gland activity. 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 in COPD patients. 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 alterations 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.

Conflicts of interests. Author declares the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Information about author

Marilia Sukholytka
Department of respiratory medicine, Thomayer hospital, Prague, The Czech Republic; e-mail: info@ftn.cz

Accepted 01.12.2020

Revised 24.11.2020

Received 06.11.2020

Резюме.
Гипотиреоз и хроническая обструктивная болезнь легких

Ризик хроничнії обструктивної хвороби легень (ХОБЛ), а також захворювання цитоїдної залози зростає з віком. ХОБЛ — загальне системне захворювання, пов’язане з хронічним запаленням. Багато ендокринологічних розладів, включаючи захворювання цитоїдної залози, пов’язані із системним запаленням. Епідеміологічні дослідження показують, що в пацієнтів із ХОБЛ підвищений ризик розладів цитоїдної залози. Ці асоціації недостатньо вивченні, і тиреоїдні захворювання не включені до загальнозвизнаного спіску супутніх захворювань ХОБЛ. Водночас вони можуть значно погіршити якість життя хворих на ХОБЛ. На жаль, діагностика досить складна, оскільки багато ознак маскуються симптомами основного захворювання. З’ясування кореляції між захворюваннями цитоїдної залози та ХОБЛ сприятиме кращій допомозі особам із такою патологією. У цьому огляді проаналізовано доступну літературу, що описує існуючі зв’язки між ХОБЛ та захворюваннями щитоподібної залози.

Ключові слова: гипотиреоз; хронічна обструктивна хвороба легень; коморбідність; цитоїдна залоза; огляд

Гипотиреоз и хроническая обструктивная болезнь легких

Резюме. Риск хронической обструктивной болезни легких (ХОБЛ), а также заболеваний щитовидной железы увеличивается с возрастом. ХОБЛ — общее системное заболевание, связанное с хроническим воспалением. Много эндокринологических расстройств, включая заболевания щитовидной железы, связаны с системным воспалением. Этиологические исследования показывают, что у пациентов с ХОБЛ повышенный риск расстройств щитовидной железы. Эти ассоциации недостаточно изучены, и тиреоидные заболевания не включены в общепризнанный список сопутствующих заболеваний ХОБЛ. В то же время они могут значительно ухудшить качество жизни больных ХОБЛ. Следовательно, диагностика довольно тяжелая, поскольку многие признаки маскируются симптомами основного заболевания. Выведение корреляции между заболеваниями щитовидной железы и ХОБЛ будет способствовать лучшей помощи лицам с такой патологией. В этом обзоре проанализирована доступная литература, описывающая существующие связи между ХОБЛ и заболеваниями щитовидной железы. Признаки или симптомы пониженной функции щитовидной железы могут быть неспецифическими, особенно среди пожилых людей, поэтому дифференциальная диагностика между симптомами ХОБЛ и симптомами, связанными с захворявшимися щитовидной железой, может викликати трудности. Багато даних свідчать про більш високий риск зміни функціонального стану цитоїдної залози у хворих на ХОБЛ. Гипотиреоз може впливати на дихальну функцію різними механізмами, навіть в осіб із інтактною дихальною системою. Тому складно розрізнити, чи є гормональні зміни причиною або наслідком різних ознак або симптомів порушення дихання. У деяких випадках корекція гормональних змін може покращити якість життя хворих на ХОБЛ і інші наслідки захворювання. Установлення взаємозв’язків між ХОБЛ, функцією цитоїдної залози та тиреоїдними розладами може надати важливу інформацію про системний природу ХОБЛ.

Ключевые слова: гипотиреоз; хроническая обструктивная болезнь легких; коморбидность; щитовидная железа; обзор