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Obstructive sleep apnea syndrome and hypothyroidism — merely concurrence or causal association?

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Abstract

The prevalence of obstructive sleep apnea-hypopnea syndrome (OSAHS) ranges from 4 to 7% in men and from 2 to 5% in women. Its deleterious consequences such as traffic accidents, cardiovascular complications increasing morbidity and mortality, make it a major health problem. Apart from obesity (a major risk factor for OSAHS), hypothyroid patients are prone to reveal this phenotype. Although hypothyroidism seems an acknowledged risk factor for OSAHS, some authors report the lack of clinically relevant association. The argument partly depends on the increased prevalence of hypothyroidism in OSAHS patients, but the epidemiological data is limited and somehow inconsistent; even less is known about sub-clinical hypothyroidism in OSAHS patients. Even if frequency of overt and sub-clinical hypothyroidism in OSAHS patients is comparable to the general population, screening for it seems beneficial, as hormone replacement therapy may improve sleep disordered breathing. Unfortunately, this favorable outcome was found only in a few studies with limited number of patients with hypothyroidism. Yet, despite the lack of international guidelines and no large multicentre studies on the topic available, we think that TSH screening might prove beneficial in vast majority of OSAHS patients.

Key words: subclinical hypothyroidism, hypothyroidism screening, obstructive sleep apnea-hypopnea syndrome, thyroid, sleep
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Obstructive sleep apnea-hypopnea syndrome

Obstructive sleep apnea — hypopnea syndrome (OSAHS) is a chronic condition, characterized by recurrent pauses in breathing during sleep. In consequence, they lead to sleep fragmentation and intermittent hypoxemia. Decreased quality of sleep leads to excessive day time sleepiness, cognitive dysfunction and impaired work performance [1]. OSAHS contributes to systemic hypertension [2], cardiovascular diseases [3] and abnormalities in glucose metabolism [4]. The reported prevalence of OSAHS in adult population ranges from 4 to 7% in men, and from 2 to 5% in women [1, 5]; with some subgroups of the population bearing higher risk [1]. It is a serious

health problem considering high prevalence and its deleterious consequences, e.g. traffic accidents or all causes related morbidity and mortality [6–8]. Polysomnography is an acknowledged gold standard in OSAHS diagnostics.

Clinical and sub-clinical hypothyroidism

Primary hypothyroidism is a condition, in which thyroxin levels in blood are reduced and are accompanied by increased levels of TSH as an effect of disruption of negative feedback mechanism. Thus, hypothyroidism is diagnosed when concentration of serum TSH exceeds 4.5 mIU/L and free T4 (FT4) concentration is below the reference range: 0.8–2.0 ng/dL (10.3–25.7 pmol/L). The reported prevalence of overt hypothyroidism

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lies within wide range — from 0.3% even up to 9.2%. The condition presents more often among women [9].

The term sub-clinical hypothyroidism has been coined for a condition defined as serum TSH concentration above the upper limit of the reference range (4.5 mIU/L) with serum free T4 (FT4) concentration within normal range (usually low normal) [10]. The prevalence of sub-clinical hypothyroidism is higher than the overt one and ranges between 3% and 18% in the adult population [11].

There is a substantial risk of 2 to 6% yearly for the progression of sub-clinical hypothyroidism to the overt one, with females being at higher risk. Other factors that may predispose to the progression include: higher levels of TSH and presence of antithyroid peroxidase antibodies. On the other hand, TSH levels normalize spontaneously in 15 to 65% of cases with elevated TSH found in a single blood sample (follow-up periods lasting 1 up to 6 years). Conversely to progression to overt hypothyroidism, a spontaneous recovery is more likely with individual TSH levels < 10 mIU/l [10].

As numerous studies have shown, there are several risk factors for overt and sub-clinical hypothyroidism. These include gender, with women being more vulnerable than men [12, 13]. Another factor that may influence the level of serum thyrotropin is age — up to 18% of elderly suffer from this condition [11]. When these two factors overlap the prevalence of hypothyroidism among women over 60 years old may reach up to 24% [14]. Interestingly, populations that are sufficient in iodine are more prone to sub-clinical hypothyroidism [11]. Continuing, some studies suggest that in areas, where diet is deficient in iodine, serum TSH levels greater than 5 mIU/L are rare (1.5% among women over 60 years old) [15]. Other studies point to the same factors as determinants of higher risk for sub-clinical thyroid disease including pregnant women and women older than 60 years [10].

Association of OSAHS and hypothyroidism

There is a great variance in reported prevalence of hypothyroidism among patients with OSAHS. Namely, it has ranged from 2% to 11% [16, 17]. OSAHS and hypothyroidism have similar symptomatology, which creates a significant risk for misdiagnosis. Moreover, hypothyroidism is a risk factor for OSAHS and one of a few causes thereof amenable to treatment. In effect, a hypo-

thyroid patient with secondary apneas may be misdiagnosed with primary OSAHS. Symptoms and signs common in both conditions include: obesity, fatigue, decreased libido, depressed mood, impaired concentration, snoring and witnessed apneas. The overlap in clinical presentation, creates a significant risk for OSAHS diagnosis among patients referred to sleep clinic who, actually, have undiagnosed hypothyroidism [17, 18].

Numerous papers address the relationship between OSAHS and hypothyroidism. Although hypothyroidism is an acknowledged risk factor for OSAHS, some controversy lingers, mainly due to studies that report the lack of clinically relevant association [16]. Moreover data on association between OSAHS and sub-clinical hypothyroidism are insufficient. In this case the differentiation may be even harder as individuals with sub-clinical hypothyroidism are often pauci-symptomatic, and clinical presentation can include non-specific complaints and symptoms, partly similar to those seen in overt hypothyroidism, such as fatigue, weakness, weight gain, cold intolerance, and constipation [19]. Therefore, the opinions on necessity for clinical and sub-clinical hypothyroidism screening in sleep apnea patients are divided into for and against positions.

Skjodt et al. [17] performed polysomnography and biochemical screening towards hypothyroidism in 200 patients. Out of 124 patients, who were diagnosed with OSAHS (69%), only 3 were also discovered to have previously undiagnosed hypothyroidism. These patients, were not included in the group treated with CPAP for the primary sleep apnea. Instead, they were treated with thyroxin therapy alone for their primary medical problem, which resulted in resolving sleep apnea — from ex-juvantibus inference a secondary one. The authors concluded that biochemical screening for hypothyroidism is required to prevent inadvertent misdiagnosis of hypothyroid sleep-disordered breathing as primary sleep apnea [17]. Nevertheless, this study is a case series report and the conclusions drawn should be viewed with caution.

Rosen D. in his study presents a case of 5-year old child with Down Syndrome diagnosed with mild to moderate OSAHS. Subsequently to this diagnosis, biochemical screening for hypothyroidism was performed. Result showed that the child was suffering from severe hypothyroidism, which caused secondary sleep apnea. After 3 months of treatment with Levothyroxine resolution OSAHS was observed. The researcher

used this study to make a point that routine thyroid function screening is not recommended. However, if a patient belongs to a high risk group of hypothyroidism it is important to pursue this diagnosis, as its treatment may bring partial or full resolution of OSAHS [20].

Similar investigations were carried out by Bahammam et al. in order to assess the concurrence of OSAHS and hypothyroidism. Moreover, in this study differentiation into clinical and sub-clinical hypothyroidism was introduced. Overall, among 254 patients, who were diagnosed with OSAHS, only 1 was newly diagnosed with overt hypothyroidism, but 26 had been previously diagnosed and were on thyroxin replacement therapy. Whereas, sub-clinical hypothyroidism, was diagnosed in 27 (10%) OSAHS patients. None of these patients had typical symptoms or signs of hypothyroidism apart from daytime fatigue and snoring. The prevalence of sub-clinical hypothyroidism was 13.7% and 7.7% in female and male OSAHS patients, respectively. Authors suggested that the prevalence of newly diagnosed cases of clinical hypothyroidism in OSAHS patients was too low to justify routine screening, unless hypothyroidism was suspected on the basis of symptoms or signs [12]. Although sub-clinical hypothyroidism was relatively common in this population, it is arguable whether this necessitate routine screening, as the clinical relevance thereof is not yet clarified.

Another study, whose findings support screening for sub-clinical and clinical hypothyroidism was conducted by Ozcan et al. It included 203 patients with mild to severe OSAHS. On evaluation of the thyroid function, 11% ($n = 22$) of the patients were found to have sub-clinical hypothyroidism and 2% ($n = 4$) overt hypothyroidism. There was no significant correlation between thyroid functions and severity of OSAHS, but due to the low number of cases the study was probably underpowered. Nevertheless, the researchers suggested that evaluation of the thyroid functions was warranted in patients with OSAHS which seems not well supported by the results of this study [21].

In a study by Mete et al. [22] a group of 150 patients diagnosed with OSAHS and 32 control subjects were submitted to functional and ultrasonographic examination of thyroid gland. The authors did not find any difference in the prevalence of hypothyroidism, numbers of nodules, and parenchyma heterogeneity determined by ultrasound, between OSAHS patients and controls. Akin to the previous one, this study seems also

underpowered due to the low number of cases per study group, especially unbalanced number of controls.

Bozkurt et al. [23] conducted a study, on the prevalence of Hashimoto's thyroiditis (HT), the most prevalent cause of hypothyroidism in populations with adequate iodine supply, in 245 euthyroid individuals, who were suspected of having OSAHS. Diagnosis of HT was based on thyroid ultrasound and serum anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies. HT was diagnosed in 32% of controls and in 47% of all OSAHS patients. Severe OSAHS patients had higher HT frequency (52%) compared to other groups, while in a group of severe female OSAHS patients it was the highest (73%). The study showed that OSAHS patients presented higher HT prevalence, which correlated with the severity of OSAHS, and the association was stronger among women. Authors of the study pointed out that screening for thyroid disorders, not only for hypothyroidism but also for auto-immune thyroid diseases in OSAHS patients may be of benefit for early diagnosis of a thyroid failure. What is more, they suggested that OSAHS may be a pathogenic factor for thyroid auto-immunity [23]. However, this statement is controversial and should be treated merely as a hypothesis and not a conclusion supported by results of the study.

Putative mechanisms of the association between OSAHS and hypothyroidism

There are several mechanisms that may play a role in association of OSAHS and hypothyroidism. The proposed mechanisms for the relationship between OSAHS and hypothyroidism include the deposition of mucoproteins in the upper airway causing upper airway obstruction, disturbances of the regulatory control of pharyngeal dilator muscles due to neuropathy, and the possibility of respiratory center depression [24].

Individuals with sub-clinical hypothyroidism suffer more often from weakness and myalgia, and reduced muscle strength has been shown in these individuals, which may result in insufficient strength of skeletal muscles that are essential to regular ventilation or upper airways patency [25, 26]. Moreover, large goiters present in some patients with hypothyroidism alone can cause pharynx occlusion and thus OSAHS [27].

Implications for treatment

CPAP (continuous positive airway pressure) is a standard treatment for OSAHS. However, in case of secondary OSAHS in the course of

hypothyroidism this may hardly revert apneas and hypopneas by securing upper airways patency, but not affecting the underlying pathology. Therefore, treating sleep disordered breathing with CPAP does not solve the problem of primary hypothyroidism. Conversely, in many cases, replacement therapy with thyroxin does not always prove enough to resolve sleep disordered breathing in patients with hypothyroidism. The clear recommendations on the treatment options, i.e. thyroxin alone or in combination with CPAP cannot be given as the data from clinical studies are limited. Skjodt et al. reported that 3 patients suffering from secondary sleep apnea were successfully treated with thyroxin therapy alone with simultaneous resolution of sleep-disordered breathing, nocturnal hypoxia, and thyroid deficiency [17]. Contrary, Mickelson et al. found that thyroid replacement therapy resulted in little or no improvement in sleep disordered breathing in 4 patients with clinical hypothyroidism [28]. Hence, introduction of thyroxin replacement therapy should be considered as a viable choice of treatment for OSAHS putatively secondary to hypothyroidism. However, it is advised that follow up in regard to sleep disordered breathing in patient undergoing such a treatment ought to be performed. If OSAHS symptoms or better, objectively monitored apneas don't disappear following a few months of hormone therapy, CPAP should be introduced as a next step. However, one has to bear in mind that these conclusions were based on studies being effectively case reports or case series due to the low number of cases and thus may be severely biased and not applicable to the general population.

When it comes to sub-clinical hypothyroidism most experts and societies suggest treatment of sub-clinical hypothyroidism if TSH levels are >10 mIU/l based on the available evidence, while taking into consideration other risk factors such as the presence of goiter, anti-thyroid antibodies, presence of cardiovascular risk or continuing clinical symptoms [10]. However, it is important to initiate treatment only after three to six months of follow-up given the high rate of spontaneous normalization of elevated TSH levels. It is mostly due to that fact that risks of treatment have been mainly associated with overtreatment, which is reported in 14% to 21% of sub-clinically hypothyroid individuals on thyroxin replacement therapy [11]. Whether the treatment of sub-clinical hypothyroidism can influence concurrent OSAHS is dubious, since there is no reliable data supporting more frequent occurrence of sub-clinical hypo-

thyroidism in apneic patients, not to mention data in favor of sub-clinical hypothyroidism as a risk factor for OSAHS. Therefore, it seems preferable for patients with OSAHS and sub-clinical hypothyroidism to focus on symptomatic treatment of apneas with CPAP and follow-up of TSH levels.

Conclusions

As there exists an overlap in clinical presentation of primary OSAHS and hypothyroidism, it is currently discussed whether screening for hypothyroidism is needed. Available data from literature does not offer definite recommendation in favor of the routine screening.

Routine screening for thyroid disorders may prevent misdiagnosis and allows physicians to find primary condition and start hormone replacement therapy, inhibiting the progression of the primary disorder. In a few cases treatment of hypothyroidism as a primary condition resulted in significant improvement of coexisting OSAHS. On the other hand, several authors point out the lack of substantial evidence for higher prevalence of hypothyroidism among patients suffering from OSAHS. Hence, they argue, there is no reason for the routine screening in this group of patients.

However, there is plausible middle ground between these opposite stances. It is reasonable to advise routine screening tests for thyroid disorders in patients that belong to a high risk group (i.e. older women) or are overtly symptomatic. Moreover, an argument in favor of screening for thyroid disorders is an early diagnosis, which can prevent long term metabolic consequences and potentially deleterious exacerbation of the condition. Also, although the prevalence of overt or sub-clinical hypothyroidism in OSAHS patients may not be increased, finding a subgroup of patients feasible for causal treatment may be a pro argument for the routine screening [17]. For practicing physicians it seems important to remember that hypothyroidism may be a reversible cause of OSAHS and that OSAHS may be a risk factor for hypothyroidism, though it is only an unproven hypothesis [27]. Yet, despite the lack of international guidelines and no large multicentre studies on the topic, we think that TSH screening might prove beneficial in majority of OSAHS patients, with the caveat that cost-effectiveness of such recommendation has not been addressed so far. This conclusion might be of value, regardless the existence of a causal association or just a concurrence of OSAHS and hypothyroidism.

This review is based on a limited number of studies with limited number of patients. Therefore, the conclusions drawn should be considered as preliminary. Long-term, large group follow-up studies are needed to establish the possible significance of routine evaluation of OSAHS patients for thyroid diseases.

Conclusions

1. Limited and somewhat contrary data on the prevalence of hypothyroidism in OSAHS population prevent drawing clear conclusions on existing association.
2. Hypothyroid patients are prone to reveal OSAHS phenotype but probably early diagnosis and effective thyroxin treatment prevent the overrepresentation of these patients in OSAHS patients.
3. Screening for hypothyroidism in OSAHS patients can potentially be rewarding as treatment of hypothyroidism may ameliorate secondary OSAHS.

Conflict of interest

The authors declare no conflict of interest.

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