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REVIEW PAPER

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Complex relationships between endocrinopathies and obstructive sleep apnea syndrome

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ABSTRACT
Sleep-related disordered breathing (SRDB) is a term covering a heterogeneous group of conditions with a similar clinical picture yet different pathogenesis. Nocturnal episodes of obstructive apnoea, leading to repeated periods of desaturation and re-oxygenation, activate chemoreceptors and increase the activity of the sympathetic as well as renin-angiotensin-aldosterone system. Moreover, the generation of free radicals and proinflammatory cytokines increases. All the above mentioned disturbances interfere with the function of endocrine glands. On the other hand, many endocrine disorders are associated with an increased risk of obstructive sleep apnoea syndrome (OSAS). In this paper, we discuss relationships between selected endocrinopathies and OSAS.
Keywords. obstructive sleep apnea, endocrinopathies, diabetes

Introduction

Sleep-related disordered breathing (SRDB) is a term covering a heterogeneous group of conditions with a similar clinical picture yet different pathogenesis. They are connected not only with a worse than normal quality of life but also with a substantial risk of numerous cardiovascular and metabolic complications that can lead to premature deaths.[1] Obstructive sleep apnoea syndrome (OSAS) is the most common type of breathing disorder during sleep. The syndrome is characterised by repeated episodes of apnoea and/or hypopnoea with preserved respiratory effort (which differentiates obstructive from central apnoea). The structure of sleep is impaired - lack of deep and rapid eye movement phases. Thus, the quality of sleep is poor and does not provide full rest, which results in excessive daytime sleepiness and chronic fatigue. One of the major factors predisposing to the development of obstructive breathing disorders is obesity and resultant accumulation of adipose tissue around the neck.[2]

Nocturnal episodes of apnoea, leading to repeated periods of desaturation and re-oxygenation, activate chemoreceptors and increase the activity of the sympathetic as well as renin-angiotensin-aldosterone system. Moreover, the generation of free radicals and proinflammatory cytokines increases. All the above mentioned

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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disturbances interfere with the function of endocrine glands.[3] On the other hand, many endocrine disorders are associated with an increased risk of OSAS.

Aim

The main aim of the study was to review the literature on relationships between selected endocrine disorders (i.e., dysfunction of thyroid, parathyroid, adrenal glands, acromegaly, diabetes mellitus) and OSAS.

Description of the study literature

Comprehensive searches of the MEDLINE (accessed by PubMed) database was performed. The following key words were use: obstructive sleep apnea, thyroid, parathyroid, vitamin D, osteoporosis, adrenal, Cushing's disease, diabetes). Articles published between January 2000 and June 2017 were included.

Analysis of the literature

Epidemiology of obstructive sleep apnoea

The prevalence of OSAS in the adult population is estimated at 4% among men and 2% among women.[4] In Poland, OSAS affects almost 1.5 million individuals. In view of the increasing prevalence of obesity in developed countries, a further increase in OSAS incidences can be expected.

Disorders of thyroid function

OSAS is likely to develop in up to 30% of patients with newly diagnosed hypothyroidism.[5] Its incidence at concomitant hypothyroidism increases, which is associated with obesity, macromegaly, impaired upper airway function, tissue deposition of mucopolysaccharides and disturbed respiratory drive regulation.[6]

The findings reported by Rest et al. have demonstrated frequent cases of subclinical hypothyroidism in patients with obesity and breathing sleep disorders. The incidence of undiagnosed subclinical hypothyroidism in the population studied was 11.5%.[7]

According to Petrone et al., thyroid dysfunction was found in almost 1/5 of patients with moderate and severe OSAS (subclinical hypothyroidism was diagnosed in 8% and low triiodotyronin syndrome in 10.4%). In patients with low concentration of fT3, lower mean values of nocturnal saturation were observed; after the 5-month continuous positive airway pressure therapy, the concentration of fT3 normalised. The beneficial effect of CPAP therapy was also found in patients with subclinical hypothyroidism - a substantial decrease in TSH levels. Interestingly, in patients with OSAS and normal thyroid function, the CPAP therapy did not cause significant changes in concentrations of THS and thyroid hormones.[8]

Jha et al. analysed the incidence of OSAS in patients with the diagnosis of primary hypothyroidism. OSAS defined as the apnoea-hypopnoea index (AHI) ≥ 5, was present in 15 patients (30%) at the beginning of the study and was reversible in 10 out of 12 patients evaluated after levothyroxine treatment (p = 0.006). The substitutive treatment with levothyroxine was associated with improved airway patency associated with reduced tongue enlargement (4 [33%] vs. 1 [8%], p = 0.083), mucous oedema (5 [42%] vs. 1 [8 %], p = 0.046) and facial oedema (10 [83%] vs. 1 [8%], p = 0.003).[9] The authors have concluded that reversible OSAS is common among patients with primary hypothyroidism and the hypothyroidism-induced changes in the upper airway anatomy are likely to contribute to the development of OSAS in such patients.

Disorders of parathyroid function, vitamin D_3 and calcium-phosphate metabolism

The episodes of hypoxaemia and hyperoxia occurring cyclically in OSAS patients can cause metabolic acidosis, negatively affect bone tissue metabolism and impair bone micro-architecture. The studies have demonstrated that hypoxaemia can favour the development of osteoporosis by blocking the growth and differentiation of osteoblasts and simultaneously stimulating the formation of osteoclasts.[10,11]

Analyses have shown significantly lower values of bone mineral density (BMD) and T-scores in the femoral neck of patients with OSAS. The serum level of β-CTX (C-terminal telopeptide of the alpha chain of type 1 collagen) was found to be statistically significantly higher in the group of OSAS patients (p = 0.017). The findings of meta-analyses have demonstrated that the mean levels of SpO2 were significantly correlated with the levels of osteocalcin and BMD. Therefore, patients with OSAS may represent a risk group with respect to loss of BMD and bone resorption.[12]

A large-scale population-based study carried out by Chen et al. has shown that OSAS is independently related to osteoporosis. Having considered age, gender, hypertension, coronary disease, obesity, stroke, hyperlipidaenia, chronic renal disease, gout, incomes and geographical regions, the OSAS patients were found to be 2.7-fold more prone to the risk of osteoporosis (adjusted HR 2.739 at 95% CI 1.690 to ~ 4.437).[13]

Recent studies have demonstrated lower concentrations of vitamin D_3 and higher levels of parathyroid hormone (PTH) in OSAS patients. Obesity affecting the majority of OSAS patients is in itself the factor favouring vitamin D_3 deficiency.[14] The available data suggest a reverse correlation of 25(OH)D with diabetes mellitus and metabolic syndrome and a positive correlation of PTH with obesity and arterial hypertension in OSAS patients.[15]

According to Liguori et al., patients with OSAS had significantly lower concentrations of vitamin D_3

and elevated levels of PTH at unchanged differences in calcaemia, compared to the control group. In the multi-factorial analysis, once disturbing variables (e.g. obesity) were accounted for, an independent correlation was observed between the level of vitamin D_3 and minimum nocturnal saturation. The short-term CPAP therapy (seven nights) resulted in a significant increase in vitamin D_3 concentrations, as compared to baseline values. Intriguingly, however, this beneficial effect was observed only in the subgroup of male patients responding to CPAP therapy (defined as AHI <5/h), and not in the subgroup of female patients, even when the CPAP treatment outcomes in them were good.[16]

Chronic vitamin D deficiency can increase the risk of OSAS by favouring tonsil hypertrophy, airway myopathy, and chronic rhinitis. Moreover, the available study findings suggest that low levels of vitamin D increase the risk of cardiovascular diseases, diabetes mellitus and autoimmune diseases. Therefore, proper concentrations of vitamin D in serum of OSAS patients can alleviate this syndrome and prevent the risk of cardiovascular diseases and diabetes mellitus.[17]

Disorders of hypothalamic-pituitary-adrenal axis

The results reported by Kritikou et al. suggest that OSAS in non-obese men and slightly overweight women is associated with the hypothalamic-pituitary-adrenal axis activity (as in obese patients with OSA). The short-term CPAP treatment substantially reduced the level of cortisol compared to the baseline values, which suggests that CPAP is likely to have protective effects in such cases.[18]

The aim of the study by Carneiro et al. was to analyse the function of the hypothalamic-pituitary-adrenal axis and results of ambulatory blood pressure monitoring (ABPM). A 24-hour ABPM and cortisol suppression testing with 0.25 mg of dexamethasone were carried out in 16 obese male patients with OSAS and 13 male individuals without OSAS. After the 3-month CPAP therapy, nine patients with OSAS were re-evaluated. The baseline decrease in systolic pressure at night in OSAS patients was lower ($p = 0.027$) and heart rate higher ($p = 0.022$), as compared to controls; moreover, the level of cortisol in saliva was found to be higher after inhibition with dexamethasone ($p = 0.001$). However, no difference in arterial blood pressure was observed ($p = 0.183$). Higher cortisol suppression was positively correlated with improved apnoea/hypopnoea indices during CPAP therapy ($r = 0.799$, $p = 0.010$).[19]

According to Wang et al. research, patients with Cushing's syndrome are at high risk of OSAS develepoment (HR = 2.82; 95% CI: 1.67–4.77) in later life.[20]

Acromegaly

Acromegaly has been recognised a risk factor for OSAS.[21-23] In the study by Weiss et al., the incidence of OSAS in patients with acromegaly was 75%. The independent predictors of OSAS included increased activity of acromegaly, older age and larger neck circumference. There was no correlation found between OSAS versus BMI and abnormal ENT results.[24] In turn, Sesmilo et al. found that patients diagnosed with OSAS had symptoms of acromegaly (1.35 cases per 1000).[25] Acromegaly may be a factor influencing the low effectiveness of CPAP.[26]

Furthermore, Grunstein et al. analysed the effects of octreotide therapy on OSAS with concomitant acromegaly. During the therapy, the indices of apnoea severity improved. As the study results show, sleep apnoea can either persist in some patients despite normalisation of growth hormone levels or significantly improve at only partial biochemical remission.[27]

Diabetes mellitus

OSAS very commonly coexists with type 2 diabetes. In the study by Foster et al., OSAS with AHI ≥ 5 events/h was confirmed in over 86% of patients with type 2 diabetes. The mean AHI was 20.5 ± 16.8 events/h. In total, 30.5% of patients had moderate OSAS (15 ≤ AHI <30) and 22.6% – severe OSAS (AHI ≥ 30). The waist circumference (OR 1.1 at 95% CI 1.0–1.1, $p = 0.03$) was significantly correlated with OSAS. The risk of severe OSAS was significantly higher in individuals with higher BMI (OR1.1 at 95% CI 10.–1.2, $p = 0.03$)[28].

OSAS is associated with enhanced insulin resistance, impaired glucose tolerance and increased risk of type 2 diabetes.[29, 30] Peng et al. showed that patients with OSAS had higher postprandial glucose concentrations than controls without sleep apnoea.[31]

From the clinical point of view, observations suggesting acceleration of microangiopathic complications are essential in patients with diabetes and OSAS, especially nephropathy and diabetic retinopathy.[32-35] Chang et al. have demonstrated that the incidence of severe OSAS is associated with increased risk for advanced stages of diabetic retinopathy (proliferative retinopathy, macular edema).[36] Altaf et al. have observed that OSAS is an independent risk factor for progression to proliferative retinopathy.[37] In recent years, the relationship between OSAS and the risk of diabetic neuropathy has also been observed.[38]

According to Babu et al., CPAP can be an effective therapeutic tool in patients with diabetes coexisting with OSAS. In their study, the duration of CPAP therapy was 83 ± 50 days, on average. In 17 patients with baseline concentrations of glycated hemoglobin above 7%, its level significantly decreased (from 9.2% ± 2.0% to 8.6% ± 1.8%). Moreover, in patients with CPAP used for more than 4 h/d, reduced levels of glycated hemoglobin were significantly correlated with the use CPAP. There was no such a correlation found in patients with CPAP used ≤ 4 h /day.[39]

Harsch at al. performed their study to determine whether OSAS is an independent risk factor for enhanced insulin resistance and whether CPAP therapy can improve insulin sensitivity. Prior to CPAP therapy, 2 days after its initiation and 3 months after effective CPAP treatment, patients were evaluated using euglycaemic clamps. The sensitivity to insulin substantially increased after 2 days ($p = 0.003$) and maintained at a stable level after 3 months of treatment. Improved insulin sensitivity after 2 days was significantly higher in patients with BMI below 30 kg/m2 than in obese patients.[40] The authors suggest that increased insulin sensitivity observed after 2 days of treatment may reflect decreasing sympathetic activity.

Conclusions

The results discussed above explicitly prove the complexity of relations between OSAS and the endocrine system. The coexistence of OSAS and endocrine disorders can mask a typical clinical image, interfere with laboratory results and make the appropriate diagnosis difficult. The CPAP therapy can affect the function of endocrine glands while the treatment of endocrinopathies can diminish the severity of OSAS.

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