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Endocrine aspects of obstructive sleep apnea

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Abstract

Obstructive sleep apnea (OSA) is a common clinical condition that has variety of adverse effects on human health. Studies suggest that OSA increases the cardiovascular risk, and a link between OSA and glucose metabolism has been described. Some endocrine and metabolic conditions (obesity, acromegaly, hypothyroidism, polycystic ovary disease, etc.) can be associated with OSA that may be improved by treatment of underlying endocrine disorders like hypothyroidism and acromegaly, where OSA is mainly related to upper airways narrowing due to reversible thickening of the pharyngeal walls. In other cases proper treatment of OSA has a beneficial effect on different endocrine disturbances. Central obesity is an important risk factor both in diabetes and sleep apnea, and recent evidence supports the direct association between them. There may be a positive feed back circle between the two disorders: sleep problems may affect endocrine function and metabolic conditions, while metabolic abnormalities potentially interfere with sleep regulation.

Key words: sleep apnea, hormonal disturbances, CPAP, metabolic syndrome, gonads, thyroid, obesity

Introduction

The term "sleep disordered breathing" refers to several different clinical disturbances. They result from a variety of pathophysiological mechanisms and affect many of the metabolic functions of human body.[1] Obstructive sleep apnea/hypopnea (OSA) is the most common of these disturbances. It is a chronic condition that is characterized by a recurrent collapse of the upper airways during sleep and leads to severe hypoxemia and frequent awakening of the patient.[2]

Approximately 4% of the adult male and 2% of the adult female population meet the current clinical and polysomnographic criteria for diagnosis of sleep apnea that require immediate treatment[3,4] and even more individuals: 24% of males and 5-9% of females have apnea-hypopnea index (AHI)>5, i.e. more than 5 episodes of apnea/hypopnea an hour,[3,4] that is the initially proposed criterion for diagnosis.[5]

The aim of this paper is to review the current information about the endocrine aspects of OSA.

Consequences of OSA

Breathing pauses that are commonly observed in OSA have several adverse consequences to the human organism including decreased saturation of oxyhemoglobin, fluctuations of blood pressure and heart rate, increased sympathetic activity, endocrine disturbances, increased brain cortex activity and sleep fragmentation.[6] Discontinuation or diminution of airflow has two main consequences. The first one is related to the fact that the patient has too many awakenings during the night that disturb sleep architecture and respectively severely decrease its effectiveness in this way leading to daytime sleepiness. Frequent awakenings combined with intermittent hypoxia result in deterioration of neurocognitive functioning and interfere with the concentration

during the day.[7] The second consequence of OSA is on the cardiovascular system. Recurrent episodes of hypoxemia may lead to tissue damage and the fluctuations of sympathetic activity during the night frequently result in hypertension when the patient is awake.[8] OSA is related to increased rate of insulin resistance and cardiovascular morbidity and mortality.[9] Many studies show the direct relationship between OSA and diseases like hypertension and diabetes mellitus that is independent of obesity.[10]

OSA and pituitary hormones

The disturbances in pituitary function in OSA patients can result from several factors besides obesity. They are related to the hypoxemia and/or sleep fragmentation, that are typical for the syndrome.[11] Compared to the patients with visceral obesity without other complications, those with obesity and OSA show marked elevation of adrenocorticotropic hormone (ACTH) in response to corticotropin-releasing hormone stimulation in combination with preserved responses of thyroid-stimulating hormone and prolactin to thyrotropin-releasing hormone. It is supposed that this ACTH-hyperresponsiveness reflects hypoxia and/or sleep disturbances induced changes in neural control of corticotroph function. It is also found that ACTH-hyperresponsiveness is not followed by rise in serum cortisol levels.[12] This corresponds to the assumption that the secretion of cortisol is partially independent of ACTH-stimulation[13,14] and reflects deeper disturbances in pro-opiomelanocortin control and pro-opiomelanocortin-related peptides such as melanocortin and agouti-related peptides. The latter take part in the control of feeding, insulin levels and body weight.[15] The lack of cortisol hyper secretion in the context of stimulated ACTH is a sign of reduced adrenal sensitivity in OSA. There is a considerably reduced response of growth hormone to provocative stimuli and decreased peripheral sensitivity to growth hormone in patients with OSA.[16] Endocrine disturbances are usually reversible during Continuous Positive Airway Pressure (CPAP) treatment.[17]

OSA can be observed in patients with some endocrine diseases such as acromegaly. In this case the changes in soft tissues, cartilages and bones at the level of craniofacial, pharyngeal and laryngeal structures may lead to upper airway obstruction during sleep.[18,19] Despite the fact that the levels of IGF-I do not correlate with AHI, the increased rate of OSA in this particular population suggests the existence of relationship to the activity of the disease.[20] It is supposed that the decreased severity of OSA during the treatment results from the reduced upper airway obstruction and diminished susceptibility to collapsing through muscle function improvement.[21]

OSA and thyroid axis

For many years it is known that on the one hand sleep disordered breathing is common in patients with hypothyroidism and on the other OSA and hypothyroidism have similar signs and symptoms. This overlapping of the clinical presentation and the fact that OSA can coexist with hypothyroidism determines the considerable risk of misdiagnosing hypothyroidism in patients with sleep disordered breathing.[23]

One study that assessed the rate of hypothyroidism in patients with OSA[24] showed that 1.6% of the patients admitted to the sleep clinic and 2.9% of the patients with OSA had hypothyroidism. In one other investigation the rate of hypothyroidism in OSA was even higher : 72 out of 95 individuals with suspected OSA undertook polysomnographic evaluation, 53 of them had OSA and 6 (11%) had hypothyroidism.[25] Replacement therapy with levothyroxine significantly reduced the severity of OSA.[26] There are studies suggesting that sleep disordered breathing could be observed in euthyroid patients suffering from autoimmune thyroid disease.[27] This is the reason why individuals with high risk or with evidence for OSA should be tested for hypothyroidism so they can get proper substitution therapy.

There are two main mechanisms by which hypothyroidism can lead to OSA : upper airway obstruction with or without obesity and suppression of the respiratory center in the brain stem.[28] W. Orr et al. suggested that the deposition of mucopolysaccharides and extravasation of proteins in the tongue and pharyngeal structures could serve as predisposing factors for OSA.[29] W. Willson and G. Bedell showed that patients with hypothyroidism changes in chest mechanics could be observed during breathing.[30]

Having in mind the high prevalence of OSA it is important weather it can affect thyroid func-

tion. In one study the level of free thyroxin (FT4) but not TSH showed negative correlation with the severity of sleep apnea.[31] In the presence of severe systemic diseases reduced conversion of FT4 to the more active hormone triiodothyronine (FT3) and a shift and increase raise of the inactive reverse FT3 (rFT3) is observed. The proper treatment of OSA leads to changes in thyroid hormones that are opposite to the described above and are typical for recovery from non-thyroid disease.[31]

OSA and adrenal axis

An assumption has been made that OSA can lead to increased activity of hypothalamic-pituitary-adrenal axis and through increased cortisol levels takes part in the pathophysiology of the metabolic syndrome and cardiovascular disease.[32,33] In order to answer this question F. Dadoun et al. carried out two independent studies. In the first one they assesed the circadian profile of cortisol in the saliva during awake state in 39 men with obesity with or without OSA and 19 normal weight control subjects.[32] The second one attempted to analyze the circadian rhythm of cortisol focusing on the night by frequent blood sampling. It included 24 men with obesity with or without OSA and 12 normal weight control subjects. The data obtained from these two studies showed that in males with obesity OSA was not related to increased diurnal cortisol levels.

Four other studies presented data on single measurements of plasma cortisol in patients with OSA or control subjects.[12,17,34,35] Only one of them[34] that used single morning measurement at 8 : 00 am found increased cortisol levels in OSA. Continous positive airway pressure (CPAP) is a method of respiratory ventilation and a "gold standard" treatment for the management of sleep apnea syndrome. Authors assumed that CPAP-treatment might have positive effect on this particular disturbance. Despite this other studies did not confirm the same conclusions.[12,17,35] R. Grunstein et al.[17] did not find increased cortisol levels in samples taken at 6 : 00 am in patients with OSA compared to control subjects. F. Lanfranco et al.[12] showed that basal morning plasma levels of ACTH and cortisol and 24-hour urine free cortisol levels were similar in men with obesity with or without OSA although no testing during sleep was performed. Besides this, CPAP-treatment did not lead to significant drop in cortisol concentration.[36]

It can be summarized that there are no definite data that OSA causes changes in hypothalamic-pituitary-adrenal axis activity. However the changes in cortisol concentration within the reference ranges show correlation to metabolic disturbances in patients with type 2 diabetes mellitus (DM2).[37] Of particular interest are the changes in cortisol levels before falling to sleep in patients with OSA after CPAP-treatment has been started. When saliva samples are taken, cortisol levels just before falling to sleep are a very good representation of lowest cortisol levels during the 24-hour period.[38] In healthy individuals this is the nadir of cortisol, which further reaches its maximum at the time of arousal.[39–41]

OSA and gonadal axis

OSA is common in middle aged men with obesity and comparatively rare in premenopausal women (ratio 6.5 : 1). In postmenopausal women that do not take hormone replacement therapy the ratio decreases significantly to 1.4 : 1.[44] It is believed that the differences in sex hormone levels are responsible for sexual dimorphism in the rate of OSA. As these levels undergo abrupt changes during puberty, pregnancy and menopause, it is possible that they modify the risk for OSA in women of different ages. There are only few epidemiologic studies directed to hormonal changes in women with OSA that are focused mainly on the menopause.[45] The significance of sex hormones has been discussed and it is thought that androgens are predisposing and estrogens are protective factor for OSA. Although sexual differences in the prevalence of OSA are attributed manly to the female sex hormones, testosterone also has its effect on ventilation.[46,47] There is evidence that testosterone has destabilizing effect on respiration during sleep.[48–50] There are reports about upper airway obstruction after testosterone administration in women.[48]

OSA and fluid-electrolyte homeostasis

Overnight production of urine usually represents $<20\%$ of the total urine for the 24-hour period in young people and about 30% in older individuals.[52] Urine production during the night is controlled by fluid intake on the one hand and

hormone secretion of vasopressin and atrial natriuretic peptide (ANP) on the other. Increased vasopressin secretion during the night leads to reduced urine volume in this period.[53] It is established that in patients with OSA nocturia is very frequent.[54] Although it can be a consequence of other disturbances, urine overproduction may result from concomitant OSA because of changes in diuretic/antidiuretic hormones during apnoic pauses.[55]

Breathing efforts during partial or complete obstruction of the airways lead to negative intrathoracic pressure that causes a fake heart volume overload signal. Hormonal response to this signal is the increase in ANP-secretion. ANP inhibits vasopressin secretion, decreases the renin-angiotensin-aldosterone system activity[56] and increases glomerular filtration rate.[57] Studies show that ANP levels are chronically increased in patients with heart failure[58] and only partially increased during the sleep apnea periods.[59]

Urine ANP levels are higher during the night and in the early morning hours in patients with AHI$>$15.[55] Although vasopressin usually rises during the night, no statistically significant changes in its levels during the 24 hour period have been observed. J. Krieger et al. showed that OSA was linked to increased daytime and overnight diuresis compared to healthy control subjects and that the frequency of miction during the night was decreased when CPAP-treatment was started.[60,61]

OSA obesity and metabolic syndrome

In the last 20 years there is evidence accumulated for different metabolic disturbances in patients with OSA. Experimental and clinical data show that OSA has an independent influence on the different components of the metabolic syndrome (MS) and its entity. On the other hand, MS and its components, especially obesity and insulin resistance or DM2, can aggravate OSA. It is proposed that OSA itself can be called a "metabolic disturbance" and so be a part of the MS.[62]

Several studies assesed the link between OSA and MS (table 1).[63–68] Coughlin et al. observed the effect of CPAP treatment in 34 men with obesity, 27 of them completing the criteria for MS, for a 6-week period.[68] They found drop in arterial pressure at awakening but no improvement in insulin resistance, lipid profile or percentage of subjects with MS.

In one recent study the authors investigated the prevalence of the MS among male Japanese patients with OSA, as well as the relationship between OSA in non-obese patients and components of the MS other than obesity (hypertension, dyslipidaemia and glucose intolerance).[78] The MS was associated with OSA in 52.4% of cases. A significant increase in the prevalence of the MS was associated with increased severity of OSA, as categorized according to AHI. In the non-obese patients with OSA hypertension, dyslipidaemia and glucose intolerance were identified in 69.3%, 42.6% and 19.8%, respectively. Non-obese patients with severe OSA had a significantly higher prevalence of two or more of these factors (55.9%).

Number of studies assesed the link between sleep apnea and the components of the MS. The sleep heart and health study included more than 6000 people at mean age 64 with sleep disordered breathing.[69] The relationship between these disturbances and many cardiovascular risk factors, including MS components has been assessed. After adjustment for age and BMI there was a significant association between AHI and waist-to-hip ratio, hypertension, hypercholesterolemia in male and decreased HDL-cholesterol and hypertriglycerdiemia in female. In Korean health and genome study, the prevalence of snoring as a sign of sleep disordered breathing had a dose-dependent relationship with MS components.[70] Most of the studies included participants with obesity, while a Japanese case-control trial studies lean males (BMI 23 kg/m^2) with OSA and individuals with no OSA selected by the amount of visceral fat mass using CT.[71] It was found that OSA is associated with hypertension, dyslipidemia, insulin resistance, fasting glucose levels and higher visceral to subcutaneous fat mass ratio. This data suggest that OSA can predispose patients to metabolic disturbances and MS even when excessive visceral obesity is not present.

Years ago MS was thought to be a syndrome of insulin resistance. OSA can aggravate insulin resistance because overnight hypoxemia blocks the central insulin receptor in the hypothalamus. Besides that OSA indirectly affects other mechanisms that contribute to the development of insulin resistance like hypertension, hypertriglyceridemia and visceral obesity thus aggravating

Table 1 Studies, assessing the association of OSA and metabolic syndrome in adults (modif.[77]).

Study	Design	Population	Main results
Coughlin et al.[63]	Case-control (matching BMI) OSA : AHI>15 Controls : AHI<5 MS : NCEP (ATP III) criteria	Male 61 OSA 43 control subjects	Idependent* relationship between : 1.OSA and MS (OR=9.1) 2.OSA and systolic and diastolic blood pressure, fasting insulinemia, triglycerides, HDL, total/HDL ratio
Gruber et al.[64]	Case-control OSA : AHI-no criteria have been shown MS : ADA criteria	38 OSA 41 control subjects	Independent* relationship between : 1. OSA and MS (OR=5.9) 2. No independent relationship between OSA and insulin resistance (measured by HOMA)
Lam et al.[65]	Population study Polysomnographic record OSA : AHI>5 MS : NCEP (ATP III) criteria	China Age 30-65 years 255 participants (150 male)	OSA and MS (OR=5.3) Independent relationship between OSA and waist, diastolic blood pressure, fasting glycemia, MS Independent factors for OSA : age, sex, BMI, MS
Sasanabe et al.[66]	Patients in sleep medicine clinics and population volunteers Polysomnographic record OSA : AHI>5 Control subjects : <5 MS according the specific criteria for Japanese population	Japan 819 OSA (719 male) 89 control subjects	Independent* relationship between : OSA and MS in males but not in females
Parish et al.[67]	Retrospective review of polisomnographic records and laboratory studies	228 consecutive patients 146 OSA 82 no OSA	Higher rate of MS in OSA patients (60 vs. 40%)
Coughlin et al.[68]	Randomized controlled transversal study CPAP treatment MS : NCEP (ATP III) criteria	34 male Mean AHI=40 Mean BMI=36 Mean age=49y.	No changes in the rate of patients with MS after CPAP treatment. Significant lowering of blood pressure

ATP=Adult Treatment Panel ; BMI=Body mass index ; CPAP=continuous positive airway pressure ; HDL=high density lipoproteins ; HOMA=homeostatic model assessment ; NCEP=National Cholesterol Education Program ; OR=odds ratio ; MS=metabolic syndrome
*after adjustment for other factors, including age and BMI.

the MS disturbances and increasing cardiovascular risk. In this way the independent contribution of OSA to the insulin resistance and glucose metabolism may affect the clinical presentation of the condition. OSA, MS and insulin resistance are closely related to BMI, waist and neck circumference.[72] Obesity is thought to be the main factor for upper airway collapse by disturbing the ventilatory control and pure mechanical reasons.

In obesity, however, there are several other mechanisms that influence OSA manifestation. Visceral fat tissue is metabolically active and it produces many proinflamatory and vasoacive

substances that play an important part in the regulation of metabolism and vascular function.[73] Central obesity is thought to be an important characteristic of MS.[74] Nevertheless a study[75] shows that sleep-disordered breathing is associated with insulin resistance independent of obesity. Although plasma adiponectin is an independent determinant of insulin resistance in OSA patients, plasma adiponectin is more closely related to obesity than to sleep apnoea. Although treatment of sleep-disordered breathing with nasal continuous positive airway pressure reportedly improves insulin sensitivity, findings suggest that treatment of obesity is also essential in ameliorating insulin resistance at least through increased plasma adiponectin levels in OSA. On the other hand, some results suggest that sleep hypoxemia may be the main determinant of circulating leptin levels, although the location of body fat deposits could contribute to the elevated circulating leptin levels in patients with OSA who are not obese.[76]

The exact mechanism of glucose metabolism disturbances in OSA is not yet completely clarified. Many factors contribute to the complicated relations between OSA, obesity and glucose metabolism. OSA itself is associated with chronic intermittent hypoxia and sleep fragmentation that may impair glucose homeostasis. Increased sympathetic activity, involvement of the hypothalamic-pituitary axis, production of reactive oxygen species and inflammatory pathway activation have been studied as mechanisms that can lead to glucose metabolism disturbances in OSA.[77]

Conclusion

Endocrine changes in patients with OSA are variable and can be both cause for and result of the sleep disordered breathing. This interaction requires complex and individual approach to each and every patient so the underlying cause can be adequately treated for reduction of the risk for complications.

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