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NEW INSIGHT INTO THE ROLE OF OBSTRUCTIVE SLEEP APNEA IN CARDIOMETABOLIC DISEASES

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Abstract

Humans spend almost one third of their life sleeping, thus sleep deprivation or poor sleep quality will have consequences upon the quality of life. Obstructive sleep apnea (OSA) is the most common sleep disorder that represents a respiratory cessation for at least ten seconds, which appears repeatable during sleep and it is accompanied by decreased oxygen saturation. The diagnosis of OSA is possible by filling in the STOP, STOP BANG, BERLIN questionnaires and performing the polysomnography, an accessible and more accurate method but yet very expensive. The prevalence of OSA is continuously increasing, but because of the nonspecific symptoms, the percentage of un-diagnosed cases is further increased. Data from 11 epidemiological studies published between 1993 and 2014 indicated an OSA prevalence of 22% in men and 17% in women. It has been suggested that there is a bidirectional causal relationship between OSA and obesity, and numerous studies have shown association of OSA with insulin resistance, diabetes mellitus, diabetic micro- and macrovascular complications and atrial fibrillation.

key words: *Obstructive sleep apnea, Obesity, Diabetes mellitus, Insulin Resistance*

Introduction

Sleep is essential for our health. Humans spend almost one third of their life sleeping, thus sleep is essential for the mental and physical functioning at high capacity. A poor sleep will damage all the body functions, involving repercussions upon the quality of life and of all social, cultural and economic areas.

The obstructive sleep apnea (OSA) or the apnea-hypopnea syndrome is one of the most common respiratory disorders. OSA involves either an interruption or a diminished air flow through upper airways, which appears repeatable during sleep, for seconds, minutes or more [1,2].

The apnea represents a respiratory cessation for at least ten seconds, which it is accompanied by decreased oxygen saturation [1,2].

Symptoms of OSA

The symptomatology of OSA is nonspecific and it can be classified in 2 categories, the daily and the nocturnal symptomatology:

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The daily symptomatology may be represented by extreme tiredness, annoying, with daily drowsiness, headache and confusional morning disposition, cognitive impairment in various degrees (lack of attention and concentration disorders on short term), personality and behavior disorders, gastro-esophageal reflux disease, hypertension and arrhythmia felt by the patient like tinitus, phosphene and palpitations; sexual dysfunction translated by decreased libido and even erectile dysfunction.

The noctural symptomatology is generally described by the family and it is represented by wheezing, snoring, episodes of breathing pauses followed by a clumsy inspiration, breathlessness sensation, stiffness, nycturia, insomnia, tireless and restless sleep [2].

The typical OSA phenotype is characterized by a BMI >30kg/m^2, a neck circumference >43 cm in men and >37 cm in women and arterial hypertension [1].

In women it was reported a lower incidence of severe OSA compared to men, the symptomatology being different for the two genders [3].

The study conducted by Basoglu OK et al. on 2827 subjects of whom 775 were women, brought in the spotlight the necessity of drawing up questionnaires to investigate the risk of OSA in women. This is necessary because the existing questionnaires fail to identify the real risk of OSA in women, the frequent symptomatology being nonspecific (behavior disorder, gastro-esophageal reflux disease, enuresis, memory loss disorders, morning headaches, insomnia) [3].

Diagnosis of OSA

Nowadays, the diagnosis of OSA is possible by filling in the STOP, STOP BANG or BERLIN questionnaires [4] and performing the polysomnography, an accessible and more accurate method but yet still expensive [5].

The use of STOP, STOP-BANG and BERLIN questionnaires represent an inferior diagnostic method of OSA compared to polysomnography, considering the fact that in 31% of the cases it does not succeed to identify the patients with severe or moderate types of OSA [6].

Using the polysomnography method one can record all phases of sleep with EEG routes [4], electrooculogram and electromyography placed on the muscles of the cheeks [1].

We can also record with the help of ECG routes the cardiac rhythm and with the anterior tibial electromyogram the involuntary movements of the legs during sleep.

A thermal sensor and an air pressure magnetic amplifier from the nasal fossa are used to evaluate the number of breaths per minute, the airflow from the mouth and nasal fosse, and the polysomnography is necessary for evaluating the oxygen saturation, but also for counting the respiratory effort too [1].

The respiratory failure may be thus classified in 3 degrees, considering the value of oxygen saturation: 1) Mild - SaO_2 90%; 2) Moderate – SaO_2 80-89%; and 3) Severe – SaO_2 < 80%.

The number of apnea/hypopnea events per hour or the apnea-hypopnea index (AHI) is useful in establishing the severity of OSA [1,2,7,8]. The severity of OSA is thus classified as follows: 1) *Absent*, AHI < 5 events/hour; 2) *Mild*, AHI ≥ 5, but < 15 events/hour; 3) *Moderate*, AHI ≥ 15, but < 30 events/hour; and 4) *Severe*, AHI ≥ 30 events/hour.

OSA prevalence and its risk factors

A review based on 11 epidemiological studies published between 1993 and 2014, shows an OSA prevalence of 22% in men and 17% in women [9].

The most recent data from Europe and USA, updated in 2016 show a continuously increasing prevalence of OSA, a percent between 14-49% of the mid-aged men being diagnosed with various severity degrees [10].

Regarding the prevalence of OSA in adults aged between 30-60 years, it is present in 9% of the women and in 24% of the men. Moderate and severe forms are found in 4% of women and in 9% of men [11].

Despite the fact that a higher number of persons with OSA is recorded, because of the nonspecific symptoms, the non-diagnosis percentage is further increased (70-80%) [11].

The potential risk factors associated with OSA are [8,11-14]:

- Family history of OSA or snoring;
- Otorhinolaryngology diseases: trachea malformations, deviated septum, hypertrophy of palatine tonsils (an increase of 3-4 times of the volume being considered significant), malformations of face configurations (maxillary malocclusion and micrognathia), malformation of the central incisors from the maxillary level;
- Gender.
- The prevalence of OSA is 2-3 folds higher in males than in premenopausal women, while in postmenopausal state OSA prevalence increases in women, with 2-3 times higher risk of OSA, the protective role of the women sexual hormones being a potential explanation. In postmenopausal women with hormone replacement therapy the prevalence of OSA is 2 times higher in those who do not follow this therapy.
- Race: the Asian race (Chinese) because of its specific cranio-facial morphology (micrognathia) shows a higher risk of developing OSA; other races exposed to this risk are represented by the Pacific Ocean population, African-Americans, US-Mexican. African-Americans and Asian races have a 2.55 times higher risk to develop OSA
- Age: the risk of OSA rises over 65 years of age, possibly secondary to a decrease in muscular tonus
- Use of sedatives
- Alcohol drinking before bedtime
- Smoking
- Metabolic diseases: obesity, especially abdominal obesity and enlarged neck circumference, insulin resistance, metabolic syndrome, diabetes mellitus (especially type 2 diabetes mellitus)
- Cardiovascular diseases: high blood pressure, cerebrovascular diseases, congestive heart failure. 50% of the patients with cardiovascular diseases have OSA at the same time and the patients with moderate and severe forms of OSA have a 2.9 higher risk to develop high blood pressure
- Other diseases: acromegaly, hypothyroidism.

OSA and obesity

OSA is associated with obesity (~70% of patients with obesity have OSA), the prevalence of OSA increasing progressively with BMI [8]. A WHO report from 2016 indicates a two fold increase in obesity cases since 1980 till present [15]. In 2014, there were registered 1.9 billion adults (39%) aged over 18 with overweight and about 600 million adults (13%) with obesity [15].

The tight interrelation between OSA and obesity and the increased number of obesity cases recorded worldwide lead to a continuous and exponential increase in the worldwide prevalence of OSA [15]. An increase in weight by 10% is associated with a six times fold increase in developing OSA, insulin resistance being one potential link between obesity and OSA [11].

Many clinical studies indicated a bidirectional causal relationship between OSA and overweight/obesity and weight loss leads to improvement of OSA in obese/overweight subjects [8,16].

OSA and type 1 diabetes mellitus

A study performed by Manin G. et al. in 2015 analyzed OSA prevalence in patients with type 1 diabetes and also the association of type 1 diabetes and OSA with the presence of micro- and macrovascular complication. The study included 67 patients with type 1 diabetes with a medium BMI of 25.8 ± 4.7 kg/m^2 [17]. Patients were tested with the polysomnography method for diagnosing OSA [17]. The study findings showed a high prevalence of OSA (49%) in these patients, 19% of them having severe OSA, respectively the interdependent association of OSA with micro-vascular complications (especially diabetic retinopathy) and macro-vascular complications [17].

Another study by Sarah S. Farabi on children, teenagers and adults with type 1 diabetes revealed the fact that those with nocturnal hyperglycemia have decreased urinary melatonin levels in comparison with the healthy subjects [18]. It is known that melatonin is the controlling hormone of sleep-awakening cycle [18], hyperglycemia having a negative influence in maintaining a normal circadian cycle. Hyperglycemia leads also to an increase in osmotic diuresis with nycturia, phenomenon that causes multiple awakenings during the night. Nowadays there is evidence for an obvious association between awakenings and poor glycemic control in these patients [18,19], sleep restriction leading to a decrease of insulin sensibility during the next day [18]. OSA in patients with type 1 diabetes is associated with unsatisfactory glycemic control, high glycemic variability, no decrease in blood pressure at night because of repeated awakenings, all accelerating the progression of cardiovascular and microvascular complications [18].

Another study by Reutrakul S et al. published in 2016, confirmed the findings reported above. Thus type 1 diabetes was associated with a poor quality sleep and a high prevalence of OSA (51.9% in adults) and a poor glycemic control in patients with severe and moderate types of OSA [20]. Even if the subjects are not obese, the patients with type 1 diabetes for more than 20 years of evolution must be investigated for the presence of OSA [21].

The study published by Banghoej AM in 2017 indicated that the prevalence of asymptomatic OSA in patients with type 1 diabetes is increased (69% of them were newly diagnosed with OSA), old age, overweight and nephropathy being associated with OSA [22].

OSA and type 2 diabetes mellitus

Nowadays, according to the relevant published literature regarding OSA, there is new proof in favor of a tight relationship between OSA and carbohydrate metabolism disorders, these two pathologies seeming to interact with each other [23]. The prevalence of OSA in type 2 diabetes mellitus patients is high, and it is considered to be an additional risk factor for the rise of cardiovascular mortality in these patients [6,24,25].

In a study conducted by Zhang P. et al. in China on a group of 880 subjects with type 2 diabetes, it was found a high overall prevalence of OSA (60%) and of moderate-severe OSA (25.6%) [11].

In everyday practice, OSA is frequently associated with type 2 diabetes, obesity and metabolic syndrome [23]. OSA and type 2 diabetes have common physiopathological pathways in developing insulin resistance [23]. OSA is an independent predictor of developing

diabetes [26], therefore screening for diabetes should be considered in patients with OSA that also present other risk factors for diabetes [2,16].

The simultaneous presence of OSA, insulin resistance, carbohydrate metabolism disorders (prediabetes, type 2 diabetes) was well established during the past years in small or large scale studies, representing nowadays an important issue in our everyday practice [24,26].

OSA is considered to be involved in the development of insulin resistance (a high risk factor for the appearance of cardiovascular disorders even in the absence of overt type 2 diabetes) with compensatory hyperinsulinism [23,24]. Patients with OSA have a low insulin sensitivity and a morning hyperinsulinism in comparison with patients without OSA [23]. The physiopathological pathways involve the presence of hypoxemia associated with an increased secretion of sympatomimetic hormones (adrenalin, noradrenalin), cortisol and a constant interruption of the night sleep [23].

The hypoxemia and the increased secretion of sympatomimetic and corticoid hormones induce a sustained increase in liver gluconeogenesis and a reduction in the muscle glucose uptake followed by the appearance of hyperglycemia [23]. This metabolic dysfunction (insulin resistance, decreased peripheral glucose utilization) is due to the sympathetic nervous system activation, the activation of oxidative stress, an abnormal function of the adreno-hypophysis hypothalamic axis, a systemic proinflammatory state (increased TNF-α, IL-6, hsCRP) [25], and increased fibrinogen and uric acid levels [23,27].

Constant interruption of sleep during the night reduces the insulin sensitivity and leads to carbohydrate metabolism disorders. Thus, these alter the vagal-sympathetic balance, activating the sympathetic nervous system during night [23].

In an independent manner regarding the volume of the adipose tissue, the severe form of OSA is associated with a higher risk in the case of unknown diabetes [28]. The presence of OSA should be screened in adults with type 2 diabetes, especially in males with obesity and history of heavy snoring and daytime sleepiness [29].

OSA and diabetes complications

OSA and diabetic peripheral neuropathy

In patients with type 2 diabetes and OSA, a 4 times increase in the appearance of diabetic peripheral neuropathy has been noticed and this is due to the reduction of oxygen saturation [8,23,30]. OSA is an independent risk factor that contributes to the appearance and the progression of this microvascular complication due to physiopathological pathways like activation of hexosamine pathway, polyol pathway, increased levels of advanced glycated products and intensification of proteinkinase activity.

OSA and autonomic diabetic neuropathy

The variability of the cardiac rhythm is considered to be a “physiological variable” of the cardiac autonomy, both of parasympathetic and sympathetic systems. It can be affected by the interaction between these 2 systems.

Diminished cardiac rhythm variability is due to an abnormal adjustment of the cardiac autonomic nervous system and is associated with type 2 diabetes, OSA, congestive heart failure and myocardial infarction [31]. Autonomic neuropathy leads to ventilator dysfunction due to the decrease of the cardiac rhythm variability [23].

OSA and diabetic retinopathy

In patients with type 2 diabetes, arterial hypertension and obesity, OSA represents an

independent and predictive risk factor for diabetic retinopathy and maculopathy [2,23].

The appearance of proliferative diabetic retinopathy is mediated through high serum levels of endothelial growth factors, proinflammatory markers along with a decreased endothelial regulatory function and high insulin resistance [23]. The mediated complement activation of the inflammatory pathways leads to high levels of C_3, high levels of NK-cell and IgM. All these are involved in the appearance and progression of the diabetic retinopathy in patients with type 2 diabetes [23]. Thus, OSA represents an independent risk factor for the presence of diabetic retinopathy [32].

OSA and diabetic nephropathy

The progression of the renal complications in OSA patients is due to hypoxemia, to the intensification of the sympathetic nervous system activity and to the proinflammatory state [23]. Recent studies show high levels of Cystatin C in patients with severe OSA. Cystatin C is considered to be a precocious biomarker of the renal lesions progression and also for cardiovascular events [23]. OSA may lead to the appearance of diabetic renal disease, with some studies reporting a relationship between the severity of OSA and the impaired renal function [23]. Other studies have shown the association between severe OSA and mild chronic kidney disease in male subjects [10].

OSA and cerebral atherosclerosis

It is well established the relationship between cerebral atherosclerosis and cerebrovascular events and the association between systemic atherosclerosis and OSA [33]. The moderate and severe OSA forms are associated with cerebral atherosclerosis. This fact was demonstrated in a study conducted by Song TJ et al. which enrolled 238 subjects diagnosed with OSA using polysomnography, angio RMN and the BERLIN questionnaire [33].

OSA and microvascular cerebral disorders

The moderate and the severe forms of OSA are correlated with the cerebral small vessels disease. This finding was reported in a study conducted by the same Song TJ et al. using the cerebral RMN and polisomnography [34]. In these patients they observed asymptomatic lacunar infarctions, micro bleedings in the cerebral substance and in the perivascular spaces [34].

OSA and atrial fibrillation

OSA is an important risk factor for arrhythmias, non-fatal or fatal ischemic cardiovascular events [27]. The prevalence of atrial fibrillation is being correlated with the severity of OSA in patients with central apnea syndrome, over 60 years of age and type 2 diabetes [35].

Conclusions

OSA remains an important sleep disorder with an incresing prevalence, being a risk factor for cardiometabolic diseases. Considering the bidirectional causal relationship between OSA and obesity, OSA should be actively identified in obese subjects to intervene on the cardiometabolic risk.

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