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Invited Review
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Controlling high blood pressure by treating obstructive sleep apnoea in patients with metabolic syndrome

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Abstract

Systemic hypertension and obstructive sleep apnoea (OSA) are frequently associated with metabolic syndrome. These comorbidities are important for the evolution, prognosis and therapeutic opportunities. In this review, the authors are aiming to analyze the epidemiological data of this combined syndrome and also to identify the benefits of continuous positive airway pressure (CPAP), weight reduction, and diet on systemic hypertension and metabolic syndrome.

Keywords: Systemic hypertension, metabolic syndrome, OSA.

Introduction and epidemiological data

Respiratory disorders play an important role in determining and increasing the rate and complication of many metabolic pathologies and cardiovascular diseases. Systemic hypertension, metabolic syndrome and obstructive sleep apnoea are emerging public health concerns. Obstructive sleep apnoea (OSA) is a disease with many associated comorbidities. This chronic disease is steadily increasing in the adult population. Between 3 and 5% of middle-aged and older women, and 10–17% of similar-aged men are diagnosed with OSA [1, 2]. OSA patients also display a constellation of metabolic and non-metabolic cardiovascular risk factors typical of metabolic syndrome with many long-term consequences [3].

Metabolic syndrome (MetSy) is a cluster often combining metabolic disorders, such as obesity, dyslipidemia, and insulin resistance, with a cardiovascular alteration such as arterial hypertension or coronary artery disease. The prevalence of the metabolic syn¬drome among men and women (ages ≥ 20 years) was 33.7% and 35.4%, respectively [4]; in black women, it was 57% higher than in black men [5]. The prevalence of moderate to severe OSA is very high (˜60%) in patients with metabolic syndrome [6]. The severity of intermittent nocturnal hypoxemia is associated with high values of triglyceride and of high-density lipoprotein (HDL) cholesterol [7]. OSA is a common comorbidity in people with type 2 diabetes mellitus (T2DM) because both OSA and T2DM are linked to a raised body mass index (BMI) and obesity sharing common pathophysiology. There are even some authors suggesting that OSA may be a manifestation of metabolic syndrome ("syndrome Z") (the typical features of the metabolic syndrome (Syndrome X) (namely central

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obesity, hypertension, diabetes, and dyslipidemia, with the addition of sleep apnea) [8]. 50% of confirmed diabetes patients have moderate or severe OSA [9]. From an epidemiological point of view, the presence of OSA is still underestimated among cardiac-metabolic disorders; there are studies reporting its presence in 67% of cases with asymptomatic coronary syndrome, and in 51.2% with metabolic syndrome [10, 11]. For the first time, in a merged population of 1853 individuals free of MetSy at baseline, studies showed that moderate to severe OSA was independently associated with a doubled risk of developing MetSy [11].

At the same time, the majority of OSA patients are hypertensive. Independently of other risk factors, they have a substantially greater risk of developing systemic hypertension (HTN) during the 4 years following a diagnosis of moderate or severe OSA [12, 13]. The risk of developing HTN was threefold greater for those with an apnoea/hypopnoea index (AHI) > 15 at baseline in population studies [12]. More than 60% of patients with resistant HTN have OSA with more than 15 apnoea/hypopnea per hour of sleep [14].

Obesity is also one of the strongest risk factors for OSA, and up to 60% of obese individuals are estimated to have OSA [15]. In the screening of hypertensive patients, Chinese authors found that 24.7% had OSA and those who smoke, those who are obese, and those who have diabetes accounted for 31.3%, 27.5%, and 16.6% of total patients, respectively [16]. Also, we must not forget that approximately 70–80% of patients with OSA are also obese [17, 18].

Pathogenic circle

Patients with sleep apnea exhibit higher levels of sympathetic nervous system activity during wakefulness as well as during sleep, relative to healthy controls [19, 20]. These apnea events induced a decrease of the oxygen and an increase of carbon dioxide levels, which activat¬ed the sympathetic nervous system. Finally, a higher level of sympathetic nervous system activity-induced blood vessel constriction, with blood pressure rising to 250/150 mm Hg. Continuous positive airway pressure (CPAP) therapy, as well as alternative OSA treatment approaches (i.e., oral appliance devices), have been shown to lower sympathetic activity in OSA subjects supporting the concept that autonomic nervous system changes are the main drive for nocturnal cardiovascular and hemodynamic alterations in sleep-disordered breathing [21, 22]. However, hypoxemia alone is not mediating HTN; Gotlieb et al. demonstrated that CPAP led to significantly greater benefit in reducing blood pressure compared to oxygen [23]. OSA increased the number of MetSy risk factors through the mediation of nocturnal hypoxia, leading to increased waist circumference and glucose levels [24]. Other prospective studies on OSA patients with hypertension found that the severity of OSA in this population does not affect the prevalence of MetSy. Specifically, they did not observe differences in triglycerides or HDL cholesterol [25. OSA reduces insulin sensitivity by 27%, 37%, and 48% according to the severity of oxygen reduction, defined as modest, moderate, or severe, respectively [26]. An increase in the apnea-hypopnea index (AHI) is associated with an increased risk for impaired glucose tolerance (IGT) and the development of insulin resistance [3]. OSA subjects also show resistance to leptin and a concomitant increase in appetite drive [27]. The presence of high but ineffective levels of leptin in obese T2DM subjects could also be a marker of insulin resistance [28]. Patients with MetSy and comorbid OSA have higher blood pressure and higher sympathetic drive compared with patients with MetSy without OSA [29]. The severity of OSA is correlated with MetSy, and arterial stiffness in obese patients and short-term weight reduction therapy improves the metabolic dysfunction and the severity of OSA and arterial stiffness, measured according to the cardio-ankle vascular index [30]. Both MetSy and OSA contribute to the destruction of the microvascular environment, increasing the risk of other cardiovascular complications such as stroke [31].

Therapy benefits

Concerning the therapeutic benefits of controlling HTN in patients with metabolic syndrome, there are many debates. CPAP is one of the treatment strategies. It was reported a reduction of blood pressure of 2-10 mmHg, but there are also studies showing a reduction of only 2-4 mmHg, probably without any clinical significance [32, 33]. The best answers are coming from patients with difficult-to-treat hypertension, with multiple antihypertensive drugs, but this depends on the compliance and adherence to CPAP of these patients (minimum 4h/per night, regularly administration [34-37]. Combined with medication and weight loss, CPAP therapy is, of course, more efficient [38]. In contrast with other evidence denying the effect of CPAP on metabolic markers, two works in connection with the European Sleep Apnoea Database (ESADA) showed improvements on metabolic variables in response to CPAP therapy. One of them demonstrated a significant decrease in cholesterol after CPAP treatment by including more than 1500 OSA patients [39]. The second one ana-

lyzed more than 1600 patients and showed a clinically relevant reduction of glycated hemoglobin levels [40]. In patients with severe OSA and metabolic syndrome, good compliance with CPAP may improve insulin sensitivity, reduce systemic inflammation and oxidative stress, and reduce global cardiovascular diseases (CVD) risk [41]. If it is combined with weight loss (change of nutrition habits) and physical activity, the effect of CPAP on HTN, level of triglycerides, and sensibility to insulin is more important in obese patients with OSA [42].

Dietary weight loss should always be combined with the treatment of OSA. The benefits are not the same. Patients who have OSA due to low arousal threshold or increased chemosensitivity may not have the same benefits as overweight and obese patients who have OSA due to increased collapsibility of their soft neck tissue [43].

Bariatric surgery, another alternative, is not always solving the cardiovascular outcomes. Chirinos et al. demonstrated that weight loss, coupled with CPAP, appeared to offer better benefits on blood pressure more important than the single interventions alone [42]. In obese patients, the severity of OSA is significantly associated with cardiovascular risk factors such as the severity of MetSy and arterial stiffness [30]. Moderate weight loss improved not only metabolic dysfunction but also the severity of OSA, helping to prevent atherosclerosis [30].

Exercise is another strategy to improve OSA and CVD. Exercise improves OSA independent of weight loss [15]. It is clearly a strategy to mitigate CVD risk, even if there is no literature supporting a causative effect of exercise on specifically improving OSA-related CVD outcomes.

Conclusions

In the future, substantial public health resources will be needed for diagnosis and early treatment of OSA but also of its association with hypertension and metabolic syndrome. Personalized therapy for each subject with the goal of normalizing the quality of life and control or delay the occurrence of comorbidities are important objectives. In addition to CPAP therapy, a comprehensive lifestyle intervention (CLI) program includes a reduced-calorie diet, exercise/increased physical activity, and behavioral counseling [44]. A CLI program that effectively achieves a weight reduction not only improves the AHI but simultaneously impacts the prognosis of coexisting diabetes [45], hypertension, and cardiovascular diseases. Adolescents with obesity are at high risk of developing MetSy and should be frequently screened for OSA to determine the need for treatment and reduce the metabolic burden [46].

Conflict of Interest

The author confirms that there are no conflicts of interest.

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