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REVIEW

Does physical exercise reduce excessive daytime sleepiness by improving inflammatory profiles in obstructive sleep apnea patients?

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Abstract
Introduction Obstructive sleep apnea syndrome (OSAS) is associated with a variety of long-term consequences such as high rates of morbidity and mortality, due to excessive diurnal somnolence as well as cardiovascular and metabolic diseases. Obesity, recurrent episodes of upper airway obstruction, progressive hypoxemia, and sleep fragmentation during sleep cause neural, cardiovascular, and metabolic changes. These changes include activation of peripheral sympathetic nervous system and the hypothalamic–pituitary–adrenal axis, insulin sensitivity, and inflammatory cytokines alterations, which predispose an individual to vascular damage.
Discussion Previous studies proposed that OSAS modulated the expression and secretion of inflammatory cytokines from fat and other tissues. Independent of obesity, patients with OSAS exhibited elevated levels of C-reactive protein, tumor necrosis factor-α and interleukin-6, which are associated with sleepiness, fatigue, and the development of a variety of metabolic and cardiovascular diseases. OSAS and obesity are strongly associated with each other and share many common pathways that induce chronic inflammation. Previous studies suggested that the protective effect of exercise may be partially attributed to the anti-inflammatory effect of regular exercise, and this effect was observed in obese patients. Although some studies assessed the effects of physical exercise on objective and subjective sleep parameters, the quality of life, and mood in patients with OSAS, no study has evaluated the effects of this treatment on inflammatory profiles. In this review, we cited some studies that directed our opinion to believe that since OSAS causes increased inflammation and has excessive daytime sleepiness as a symptom and being that physical exercise improves inflammatory profiles and possibly OSAS symptoms, it must be that physical exercise improves excessive daytime sleepiness due to its improvement in inflammatory profiles.

Keywords Obstructive sleep apnea syndrome · Physical exercise · Inflammatory profile · Excessive daytime sleepiness

Introduction

Inflammatory profiles of obstructive sleep apnea patients

Obstructive sleep apnea syndrome (OSAS) is receiving increased attention because it is associated with a variety of long-term consequences such as high rates of morbidity and mortality, mostly due to excessive diurnal somnolence and cardiovascular and metabolic diseases [1]. The mechanisms that are proposed to explain the increased cardiovascular and metabolic disease in OSAS are under investigation. In addition to obesity, recurrent episodes of upper airway

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obstruction, progressive hypoxemia, and sleep fragmentation during sleep cause neural, cardiovascular, and metabolic changes. These changes include activation of peripheral sympathetic neural activity and the hypothalamic–pituitary–adrenal axis, insulin sensitivity, and inflammatory cytokines alterations, which predispose an individual to vascular damage [2–5]

Adipose tissue, specifically visceral abdominal fat, is a rich source of inflammatory cytokines, such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) [6–8]. Previous studies proposed that OSAS modulated the expression and secretion of inflammatory cytokines from fat and other tissues. Independent of obesity, patients with OSAS display elevated levels of CRP, TNF-α, and IL-6, which are associated with sleepiness, fatigue, and the development of various metabolic and cardiovascular diseases [3, 9–11]. Vgontzas and colleagues [3] showed that these cytokines mediate daytime sleepiness and are elevated in OSA patients. Carpagnano and colleagues reported significant increases in IL-6 levels in the exhaled breath condensate of patients with OSAS compared with those in the exhaled breath condensate of obese subjects [11].

Adiponectin is a protein that is exclusively secreted by white adipose tissue with anti-inflammatory, anti-atherosclerotic, and insulin-sensitizing effects. Reduced plasma adiponectin concentration is a risk factor for cardiovascular and metabolic disorders [12]. Decreased adiponectin levels in patients with OSAS may partially explain the association between OSAS and cardiovascular disease. However, there have been conflicting reports regarding the relationship between adiponectin levels and OSAS [13–15].

Effects of continuous positive airway pressure treatment on inflammatory profiles of obstructive sleep apnea patients

Continuous positive airway pressure (CPAP) therapy is the treatment of choice for patients with severe OSAS because CPAP therapy reduces nocturnal hypoxia, sleep fragmentation, subjective excessive daytime sleepiness, and cardiovascular complications as well as enhances the quality of life that are related to OSAS [16, 17]. Moreover, some authors showed that CPAP treatment improved the inflammatory profile of OSA patients [14, 18–20].

Obstructive sleep apnea syndrome and obesity

Obesity is a risk factor for OSAS [21–24]. Previous studies demonstrated that increases in body mass index (BMI) and waist, hip, and neck circumferences were associated with a higher prevalence rate of OSAS. In a recent study in São Paulo [25], 32.9 % of 1,042 participants experienced OSAS. In addition, OSAS was detected more frequently in men (40.6 % men vs. 26.1 % in women), in age groups of more than 50 years, and in obese individuals (64.1 % frequency in individuals with a BMI that was greater than 35 kg/m^2). Therefore, the male gender, advanced age, and obesity are the main risk factors that are associated with the prevalence of OSAS. Moreover, excess weight is responsible for more than 50 % of the prevalence of OSAS [21, 22]. However, the impact of BMI in OSAS is less important in patients who are more than 60 years old [21]. Weight alterations are associated with OSAS severity [23]. In individuals without OSAS or with mild OSAS [apnea–hypopnea index (AHI)<15/h], a 10 % weight gain correlates with a six-fold increase in the risk of developing moderate to severe OSAS (AHI≥15/h) [26]. The impact of weight loss for OSAS severity has been corroborated by studies that demonstrated improvements in excessive diurnal somnolence as well as snore and respiratory events after bariatric surgery in OSAS patients [27]. Recently, Holty and colleagues [28] showed that bariatric surgery is associated with dramatic weight loss and, consequently, improvements in physical functioning and daytime sleepiness.

Effects of physical exercise on inflammatory profiles of obese patients

Physical exercise has been studied as a treatment of chronic heart diseases, obesity, and type II diabetes [29–31]. The protective effects of physical exercise against atherosclerosis and insulin resistance are well-known [29–31]. Cytokine responses to physical exercise are different from those observed in inflammatory mechanisms [32, 33]. The pro-inflammatory cytokines TNF-α and IL-1 increase with inflammation but not physical exercise [34]. During exercise, IL-6 is the predominant cytokine and exponentially increases depending on the intensity, duration, and amount of muscular mass that is involved in the exercise [35, 36]. The exercise-induced cytokine response is predominantly an anti-inflammatory response. IL-6 inhibits TNF-α production [37] and stimulates the production of the anti-inflammatory cytokines IL-10 and IL-1ra [38]. Sustained elevations in IL-6 levels are predictive for obesity and type II diabetes. However, transient fluctuations of IL-6, such as those observed during physical activity, exhibit a protective effect [39].

Compared to lean individuals, the adipose tissue in obese individuals displays increased expression of pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α, and elevated macrophage counts [40, 41]. In the adipose tissue of obese individuals, macrophages are responsible for the majority of the production of cytokines such as TNF-α

and IL-6 [40, 41]. Xu and colleagues [41] demonstrated a link between gene expression and increased inflammation in adipose tissue. In addition, they observed a dramatic increase in the insulin production in obese mice. Xu and colleagues suggested that adipose tissue was important in the development of complications that were related to obesity.

Some studies demonstrated that physical exercise correlated with an improvement of the inflammatory profile in animal model of obesity [42, 43] and in obese individuals [44, 45]. Lira and coworkers [44] studied the influence of lifestyle modifications and physical exercise in association with caloric diet in obese individuals and concluded that weight reduction was accompanied by improvements in the inflammatory profile in obese adolescent individuals.

Effects of physical exercise on the treatment of obstructive sleep apnea patients

Some authors studied the effects of physical exercise on the treatment of OSA patients. Norman and colleagues [46] showed that mild to moderate OSA patients improved subjective daytime sleepiness, the quality of life, and mood state after 6 months of a supervised exercise program. Although five of the nine patients concurrently used CPAP therapy regularly throughout the study period, all of the data were analyzed together. Norman and colleagues observed improvements in the AHI, total sleep time, sleep efficiency, and number of awakenings. Netzer and coworkers [47] evaluated the effects of a 6-month period of physical exercise that was performed twice a week for 2 h each time in 11 patients with mild to severe OSAS. The authors did not detect any significant differences in basal SpO_2 or mean SpO_2. However, the authors showed a significant decrease of the respiratory disturbance index. However, no significant changes in the rapid eye movement (REM) sleep portion of total sleep time and the total sleep time itself were observed. Improvements in patients that used CPAP therapy appeared to be associated with physical exercise. In another study, patients with OSAS were treated with CPAP and enrolled in a 6-month period of supervised physical exercise twice a week. These patients exhibited a significant decrease in the respiratory disturbance index from 32.8 to 23.6. However, no significant differences were detected in the minimum SpO_2, mean SpO_2, REM sleep portion of total sleep time, NREM sleep, or total sleep time itself [48].

Sengul and coworkers [49] showed significant improvements in AHI, health- related quality of life, the quality of sleep, and exercise capacity after 3 months of breathing and aerobic exercises three times per week in OSA patients. However, they did not detect sleepiness improvement in these patients. In addition, these patients did not use CPAP therapy in combination with exercise training. Ueno and colleagues [50] showed that 4 months of aerobic exercise three times per week improved the quality of life, AHI, minimum SpO_2, and the amount of stage 3–4 sleep in OSAS patients with heart failure.

Kline and colleagues [51, 52] demonstrated that 3 months of moderate-intensity exercise (aerobic activity and resistance training) improved depressive symptoms, vigor, physical functioning, vitality, and mental health. Moreover, the authors observed a significant reduction in AHI and the oxygen desaturation index without a significant body weight reduction. Recently, Ackel-D'Elia and colleagues [53] showed that 2 months of aerobic exercise three times per week for 1 h per session was associated with CPAP-mediated improvements in subjective daytime sleepiness, the quality of life (physical functioning and general health perception), and mood (tension and fatigue). The researchers concluded that exercise training might be used as an adjunct interventional strategy in the conservative management of OSA patients.

Some of the aforementioned results are limited by the lack of distinctions between patients that did or did not use CPAP in combination with exercise training. All of the data were analyzed together despite data indicating that some but not all patients concurrently used CPAP regularly throughout the exercise training period [46–48]. It is important to emphasize that all of these authors studied the effects of physical exercise on objective and subjective sleep parameters, the quality of life, and mood state but did not evaluate the effects of this treatment on the inflammatory profile of OSA patients.

Does physical exercise reduce excessive daytime sleepiness by improving inflammatory profiles in obstructive sleep apnea patients?

As discussed earlier, OSAS and obesity are strongly associated with each other and share many common pathways that induce chronic inflammation [54, 55]. The current evidence suggests that the protective effects of exercise may be partially mediated by its anti-inflammatory effects and that this effect has been shown in obese patients [34, 44].

It is interesting to note that some authors demonstrated that CRP, TNF-α, and IL-6 levels were elevated independent of obesity in patients with OSAS and were associated with sleepiness, fatigue, and the development of a variety of metabolic and cardiovascular diseases [3, 9, 10]. In accordance with Vgontzas and colleagues [3], these cytokines mediated daytime sleepiness and were elevated in OSAS patients independent of obesity.

Mediano and colleagues [56] investigated polysomnographic determinants of excessive daytime sleepiness (EDS) in patients with OSAS and showed that patients with

OSAS and EDS are characterized by shorter sleep latency, increased sleep efficiency, and worse nocturnal oxygenation than those without EDS. They concluded that nocturnal hypoxemia can be a major determinant of EDS in patients with OSAS. Bahammam [57] pointed out the possible coexistence of obesity hypoventilation syndrome (OHS), which is a known cause of EDS, in the Mediano studied group of patients with OSAS. This author suggests that the lower nocturnal oxygen saturation and the daytime somnolence observed by Mediano et al. in the EDS group might be due to OHS. Bahammam also concluded that low nocturnal blood oxygen saturation has a fundamental role in EDS, whether or not it is related to OHS. However, Castiglioni and colleagues [58] suggested that EDS is not always associated with low nocturnal blood oxygen saturation in sleep-related breathing disorders and that other factors are involved. These authors demonstrated an association between EDS and impaired autonomic cardiac modulation and suggested that autonomic arousals may be an additional cause of EDS. They concluded that at least two independent factors are associated with the pathogenesis of EDS in sleep-disordered breathing patients. One is a low nocturnal oxygen saturation, probably caused by OHS, and another is an enhanced sympathetic cardiac modulation at night, probably caused by repeated nocturnal autonomic arousals.

In a recent review, Vgontzas [59] concluded that there is not a correlation between OSAS severity and EDS. This finding corroborated with the authors cited above that EDS are related to other factors independently of polysomnographic findings such as AHI.

In a recent paper published by our group, Alves and colleagues [60] hypothesized that compared with conventional therapies, exercise training is a more effective strategy for counteracting OSAS, obesity, and diabetes involved in the development of sleep disorders. However, additional studies are needed to elucidate the mechanisms of how exercise training improves sleep quality. In another study, we concluded that exercise training might be used as an adjunct interventional strategy in the conservative management of OSA patients [53].

Moreover, Bixler and colleagues [61] and Basta and colleagues [62] demonstrated that the degree of physical conditioning is associated with EDS and fatigue in humans. As cited above, some authors in scientific literature [61, 62] showed that EDS may be caused by an increased sympathetic activity and/or an increased nocturnal hypoxemia.

We believe that physical exercise can modulate these two factors, in addition to directly cause improvements on inflammatory profile of individuals that present mild chronic inflammation such as obese individuals. Santos and colleagues [63], in an important review for this specific area, presented possible mechanisms of interaction among sleep, physical exercise, and cytokines. They suggested that physical exercise may alter cytokine quantity and profile and reduces the effects of cytokines on central nervous system and more directly on sleep.

It is well described in scientific literature that physical exercise may cause important alterations in sympathetic activity in patients with OSAS and in hypertensive patients. Gozal and colleagues [64] showed that regular physical activity can promote protection against adverse functional consequences of intermittent hypoxia on memory and learning activities in rats and that it is associated with a reduction of oxidative stress markers.

Therefore, in this review, we cited some studies that directed our opinion to believe that since OSAS causes increased inflammation and has EDS as a symptom and being that physical exercise improves inflammatory profiles and possibly OSAS symptoms, it must be that physical exercise improves EDS due to its improvement in inflammatory profiles. By expanding our knowledge of these issues, it is important to verify the effects of physical exercise on the inflammatory profile of OSAS patients.

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Conflict of interest No conflicts of interest are declared.

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