MINIREVIEW

Inflammation and Oxidative Stress in Obstructive Sleep Apnea Syndrome

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Similar to obesity, with which it is closely associated, obstructive sleep apnea syndrome (OSAS) is rapidly becoming a worldwide epidemic. Current knowledge of its pathogenesis has been significantly enriched by numerous experimental studies that have demonstrated an important role of oxidative stress and inflammation. Furthermore, new and exciting data strongly connect these two components in the perpetuation of the condition via the overexpression of nuclear factor κB. Experimental data support the hypothesis that nutrition might represent a promising future approach with antioxidants currently being good candidates for the modulation of cardiovascular sequelae, although weight reduction and controlled positive airway pressure remain the only established treatments for OSAS. We discuss herein the recent literature that illustrates these new paradigms and speculate on possible implications and future scenarios. Exp Biol Med 232:1409–1413, 2007

Key words: intermittent hypoxia; reactive oxygen species; animal model; dietary supplement

The Impact of Obstructive Sleep Apnea Syndrome (OSAS)

OSAS is a pathologic condition characterized by numerous hypopnea/apnea episodes during nightly sleep, secondary to complete or partial obstruction of the upper airways. The syndrome is significantly associated with frequent arousals during the night that ultimately lead to daytime sleepiness (1). It is currently estimated that one out of five adults in the United States manifests some degree of OSAS (2) and that the economic burden for OSAS cases not coming to medical attention is steadily increasing (3), thus making OSAS a major public health concern. OSAS often coexists with other epidemic conditions such as obesity and the metabolic syndrome; similar to such diseases, it is significantly associated with several cardiovascular conditions, in particular arterial hypertension, ischemic heart disease, and stroke (4), as well as type 2 diabetes and nonalcoholic fatty liver disease. The severity of the syndrome is estimated by the number of episodes of apnea/hypopnea per hour of sleep (expressed as the apnea-hypopnea index [AHI]) as mild (AHI 5–15), moderate (15–30) and severe (>30). Importantly, an AHI >11 has been identified as an independent risk factor for cardiovascular disease leading to a 1.42 risk after correction for all other confounding factors (4). Besides the major metabolic and vascular sequelae, some of the most serious consequences of OSAS include attention deficit and impaired concentration and memory (5), mainly related to OSAS-associated nocturnal hypoxemia (6). The solid link between cardiovascular disease and OSAS has prompted a vigorous research effort to define the common pathogenetic grounds that might produce such association. In particular, besides the well-known activation of the sympathetic nervous system (7), OSAS and its consequences are associated with major oxidative stress and a proinflammatory state that could in turn facilitate the onset of cardiovascular conditions

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Table 1. Available Evidence of Chronic Inflammatory Status in Human Obstructive Sleep Apnea Syndrome

Local inflammation—upper airways	
Interleukin 6	↑
CD4+ cells	↑
CD4+/CD25+ cells	↑
CD8+-activated cells	↑
Neutrophils	↑
Macrophages	↓
Systemic inflammation—peripheral blood	
C-reactive protein	↑
Tumor necrosis factor α	↑
Interleukin 6	↑
Reactive oxygen species	↑
Nitric oxide	↓

(8). Furthermore, obesity commonly characterizes patients with OSAS, thus suggesting that nutrition might play an independent role in the modulation and possibly the pathogenesis of the condition. Based on these assumptions, we discuss selected recent data on the impact of oxidative stress and inflammation on OSAS *per se* and its consequences or associated conditions. We further attempt new speculations on old and new players in this complex clinical entity with a discussion on the potential role of nutrition.

The Oxidative and Inflammatory Components of OSAS

Oxidative stress (i.e., the increase of reactive oxygen species [ROS]) causes a cytotoxic tissue injury *via* an increase in lipid peroxidation, protein oxidation, and direct DNA damage that ultimately leads to apoptosis or necrosis when the scavenging capacity of the tissue is overcome. Data from a large number of studies clearly indicate that OSAS is associated with a significant increase in several markers of oxidative stress (9, 10). Because nitric oxide (NO) is a critical determinant in the establishment of chronic oxidative stress, one key role could be played by the altered NO production that characterizes intermittent hypoxia in animal models (11). Nevertheless, it is of major interest to note that continuous positive airway pressure (CPAP) treatment produces a significant decrease in all oxidative stress biomarkers (12, 13), thus suggesting an independent causal effect of OSAS on the observed phenomena. Animal studies further support this primary role by demonstrating that nonobese rodents subject to chronic intermittent hypoxia (functional model of OSAS) develop increases in lipid peroxidation and decreases in tissue-scavenging mechanisms in both heart (14) and brain (15) tissues. Importantly, studies aimed at determining the possible role of enhanced homocysteine levels as a cofactor in OSAS-associated oxidative stress have produced conflicting results (16) despite a proposed correlation with the AHI index (17). Cumulatively, the available evidence suggests that OSAS is associated with significant oxidative stress (secondary to increased ROS production, reduced scavenging capacity, and possibly hyperhomocysteinemia) that may ultimately contribute to the sympathetic activation (7) and endothelial dysfunction (18) described in these patients. Furthermore, based on the evidence in inflammatory diseases of autoimmune pathogenesis (19), the role of ROS in determining atherosclerosis should also be considered. In fact, both oxidative stress and endothelial dysfunction might develop from chronic inflammation. Indeed, a proinflammatory state has been reported at both systemic and local (upper airways) levels in patients with OSAS, and its impact remains to be elucidated. From a generic standpoint, human studies have demonstrated that patients with OSAS manifest high circulating levels of multiple biomarkers of both systemic and local inflammation (Table 1). Increased circulating levels of proinflammatory cytokines such as interleukin 6, tumor necrosis factor α (TNFα) (20), and C-reactive protein (21, 22) appear as common findings to all studies. It is of note that TNFα also regulates lipid and glucose metabolism and is expressed by adipocytes (23), thus making obesity once again an important factor in all reported differences; however, TNFα levels are significantly reduced following CPAP (20). OSAS is also characterized by chronic inflammation with mucosal congestion of the upper and lower respiratory tracts, with the latter also presenting edema and macrophage infiltration (24). The common hypothesis states that these phenomena are secondary to the upper airway mechanical injury and systemic hypoxia, but further and more recent data indicate that its causes and consequences might be more complex than originally thought. In fact, it has been demonstrated that apnea triggers systemic inflammation by inducing changes in leukocyte function in an OSAS animal model (25), whereas sleep deprivation *per se* induced spontaneous proinflammatory cytokine production by human monocytes (26) at the same time as treatment with anti-TNFα monoclonal antibodies (etanercept) in a limited number of patients with OSAS led to a drastic amelioration in daytime sleepiness (27). The role of leptin in OSAS remains poorly defined because leptin shares similar proinflammatory activity with TNFα (28), besides its well-defined role in energy metabolism. Data in OSAS show that it is characterized by increased plasma leptin levels (29), but future research in the field clearly deserves attention. Taken altogether, the available data strongly support a role for inflammation in determining the clinical features of OSAS, although a primary pathogenetic role can only be hypothesized at present. Most recently in fact, the resulting picture has been enriched by the experimental finding that ROS share the capability to trigger the production of proinflammatory cytokines, and this is most likely mediated by the overexpression of nuclear factor κB (NF-κB) in neutrophils from patients with OSAS (30). More interestingly, such phenomena are proportional to the syndrome severity and are reversible following CPAP treatment. The observation

was also supported by data from Greenberg *et al*. (31), who reported a similar effect of chronic intermittent hypoxia. The involvement of NF-κB in the pathogenesis is not of secondary importance based on its critical role at the crossroad between inflammation and oxidative stress.

Several potential players in this scenario have been overlooked; this is the case, for example, for both the innate (represented particularly by monocytes) and acquired immunity cellular compartments in which few functional studies have been performed thus far. Quantitative data from the analysis of affected tissues, in fact, demonstrate a significant increase in the number of T cells (both CD4+ and CD8+, the latter mostly activated) (32) and of neutrophils (33) in the upper airway mucosa. Surprisingly, it remains unknown what link exists between this cell subpopulation's representation and activity and the proinflammatory milieu that characterizes OSAS. Further, new and interesting connections between inflammation and atherosclerosis are coming to light based on serum autoantibodies (34), and they should not be overlooked in OSAS.

Nutrition in the Future of OSAS?

Currently the treatment of OSAS is based on weight reduction and CPAP. Discussing the current dietary and surgical approaches for the treatment of obesity is beyond the scope of this minireview. Bariatric surgery is an effective measure that significantly ameliorates or cures OSAS in morbidly obese patients, but its indications remain limited (35). CPAP is first-line therapy for OSAS to reduce daytime sleepiness and improve cardiovascular and metabolic outcomes. More recently autoadjusting CPAP has been proposed as an alternative treatment to reduce OSAS symptoms while increasing long-term CPAP compliance. On the other hand, specific nutritional supplements have been proposed for the modulation of oxidative and inflammatory aspects of OSAS, mostly with inconclusive or disappointing results obtained from small studies. For the vast majority, supplements were chosen for their antioxidant activity, and the end points considered in their clinical evaluation were related to the cognitive decline associated with OSAS (36). This is thought to be due to the prefrontal cortical dysfunction that is caused by intermittent hypoxia episodes (5). Several methodologic difficulties stand in the way of appropriate evaluation of nutrient effects on OSAS, and they are the reason why systematic, prospective, controlled studies have not been carried out. We also note that potential anti-inflammatory approaches have been overlooked so far (37). Most evidence is thus obtained from epidemiologic and experimental studies on antioxidant supplements based on the pathogenetic background shared by OSAS and other obesity-related comorbidities (37). Among experimental evidence, it is of note that a diet rich in pro-oxidants and limited in antioxidants can exacerbate the ROS-mediated tissue injury typical of OSAS, thus contributing to cognitive decline (38). The role of nutrients in OSAS can also be determined by epidemiology for the condition itself or for the metabolic syndrome. One study, thus far published only in an abstract form, on military veterans with OSAS demonstrated a significantly lower intake of vitamin E and other antioxidants (e.g., folate, vitamin C) compared with veterans without the condition (39). On the other hand, patients with the metabolic syndrome included in the Third National Health and Nutrition Examination Survey had lower vitamin E levels, although a faster metabolism cannot be ruled out in these cases (40). More specifically, there have been studies on the role of vitamins C, E, and B, lipoic acid, folate, and coenzyme Q_{10} supplementation in patients with the metabolic syndrome, but the applicability of their results in patients with OSAS remains questionable because sleep-associated factors were not included as clinical end points in the studies (36). Most recently a beneficial effect of vitamin C on vascular function in a small number of patients with OSAS has been reported (41). To summarize, we submit that nutritional supplements might prove beneficial as adjuvant treatment for OSAS; in fact, the current management of patients remains centered on weight reduction and CPAP, yet experimental data suggest that specific nutrients might beneficially influence different aspects of OSAS pathogenesis, thus possibly modulating the short- and long-term sequelae of the syndrome.

What Comes Next?

The growing fountain of knowledge indicates that new players should be taken into account in future studies on OSAS. We are aware that, similar to what was mentioned for nutritional studies, new research to determine the impact of inflammation, oxidative stress, and nutrition on sleep patterns is difficult to design, due to numerous flaws in achieving or recapitulating solid data referred only to OSAS. As an example, one should consider that OSAS commonly associates with obesity and that adipose tissues contain a large number of macrophages. Both adipocytes and macrophages are active in the secretion of inflammatory mediators, thus contributing to the systemic proinflammatory state typical of OSAS and possibly secondary to an accelerated phenomenon of immune-risk phenotype, as observed in immunosenescence (42). In this context, the use of animal models should be encouraged, with an effort to develop new ones that manifest the clinical features of the human condition. An example of animal studies in a different aspect of the metabolic syndrome (e.g., non-alcoholic fatty liver disease) illustrates the advantages of developing comprehensive models in the study of pathogenetic mechanisms (43). Furthermore, research should focus more closely on the increasing number of nonobese subjects with OSAS. Novel interactions between basic and clinical scientists should also be encouraged. In particular, the inflammatory pathway in OSAS is the ideal setting to prove that only a combined approach will succeed in answering

the many remaining questions on OSAS. Such approaches should include an optimal clinical selection of patients and more importantly, controls, as well as the use of modern pharmacogenetic screening (44). Further, based on experimental data on its levels in OSAS (30), it has been suggested that NF-κB plasma measurement might prove helpful in clinical practice for the assessment of disease severity or compliance to CPAP; however, the data are currently too limited to support this conclusion (45).

Evidence on possible dietary intervention in OSAS remains largely incomplete, and its proposed efficacy is well within speculation. We encourage larger studies—placebo controlled, randomized, and well defined for nutritional baseline differences—to provide definitive proof of efficacy for the proposed treatments. In particular, future studies should have two main types of end points (i.e., related to basic mechanisms of disease such as inflammation and oxidative stress and to cardiovascular conditions associated with OSAS during follow-up). Among the latter, we submit that cognitive impairment and oxygen desaturation would be ideal measurements to be considered for long- and short-term studies, respectively. Further, compounds with anti-inflammatory and antioxidant activity different than the traditional ones should not be overlooked because they may provide cardiovascular benefits (19) or anti-immunosenescence activity, particularly in middle-aged women (46) for whom events early in life appear to play an important immunodeterminant role (47). These would include, for example, flavanols contained in cocoa or green tea. Although we are well aware of the potential weight effects of a cocoa-rich diet in obese subjects, data obtained in alcoholic liver disease (48), sharing the inflammatory and oxidative background of OSAS, are promising, and flavanols should not be overlooked, particularly in light of their impact on cardiovascular function (49). Similarly, other potential candidates might include compounds with anti-inflammatory and scavenging activity such as the shiitake mushroom (*Lentinus edodes*) (50).

In conclusion, OSAS represents an interesting paradigm for modern researchers because it is characterized by important social and economic pressures caused by its increasing prevalence and health-related costs and it warrants a multidisciplinary and rigorous approach for the collection of evidence. For these reasons, researchers of the metabolic syndrome are encouraged to design studies that include OSAS changes among the multiple end points for the proposed intervention while attempting to correct for all aforementioned confounding factors.

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