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Obstructive Sleep Apnoea Syndrome as a Systemic Low-Grade Inflammatory Disorder

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1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disorder characterized by recurrent upper airway collapse during sleep. A reduction or complete cessation of airflow occurs despite ongoing inspiratory efforts and leads to arousals, sleep fragmentation, and oxyhemoglobin desaturation (Remmers et al., 1978; Young et al., 1993).

Though clinically recognized for more than four decades (Gastaut et al., 1965), general awareness of OSAS has been slow to develop. OSAS has been associated with cardiovascular disease (Marin et al., 2005; Duran-Cantolla et al., 2010; Barbe et al., 2010), automobile accidents (Teran-Santos et al., 1999), chronic obstructive pulmonary disease (Chaouat et al., 1995), heart failure (Oldenburg et al., 2007) and health related quality of life deterioration (Pichel et al., 2004). OSAS often coexists with obesity and has been related to insulin resistance and metabolic syndrome (Choi et al., 2008).

Patients with OSAS experience repetitive episodes of hypoxia and reoxygenation during transient cessation of breathing that may have systemic effects. These patients also present increased levels of biomarkers linked to endocrine-metabolic and cardiovascular alterations (Zamarron et al., 2008). Moreover, OSAS may involve sleep fragmentation, tonic elevation of sympathetic neural activity, oxidative stress, inflammation, hypercoagulability and endothelial dysfunction (Bradley & Floras, 2009; Fava et al., 2011). All of this indicates that OSAS should be considered a systemic disease rather than a local abnormality.

The present review analyses the pathophysiology related to the systemic consequences of OSAS and the mechanisms involved in the association between OSAS and systemic diseases (Figure 1).

2. Sleep fragmentation

Extreme sleep habits can affect health and have been associated with increased inflammation. Significant changes in habitual sleep duration can lead to chronic low-grade systemic inflammation (Meisinger et al., 2005; Patel et al., 2009). Activation of pro-inflammatory pathways may represent a mechanism. In a recent study in pediatric OSAS patients, increased TNF-α levels were primarily driven by sleep fragmentation and body

mass index. These levels were closely associated with the degree of sleepiness, as measured by the Multiple Sleep Latency Test. Surgical treatment of OSAS resulted in significant reductions in TNF-α levels with reciprocal prolongations in sleep latency (Gozal et al., 2010).

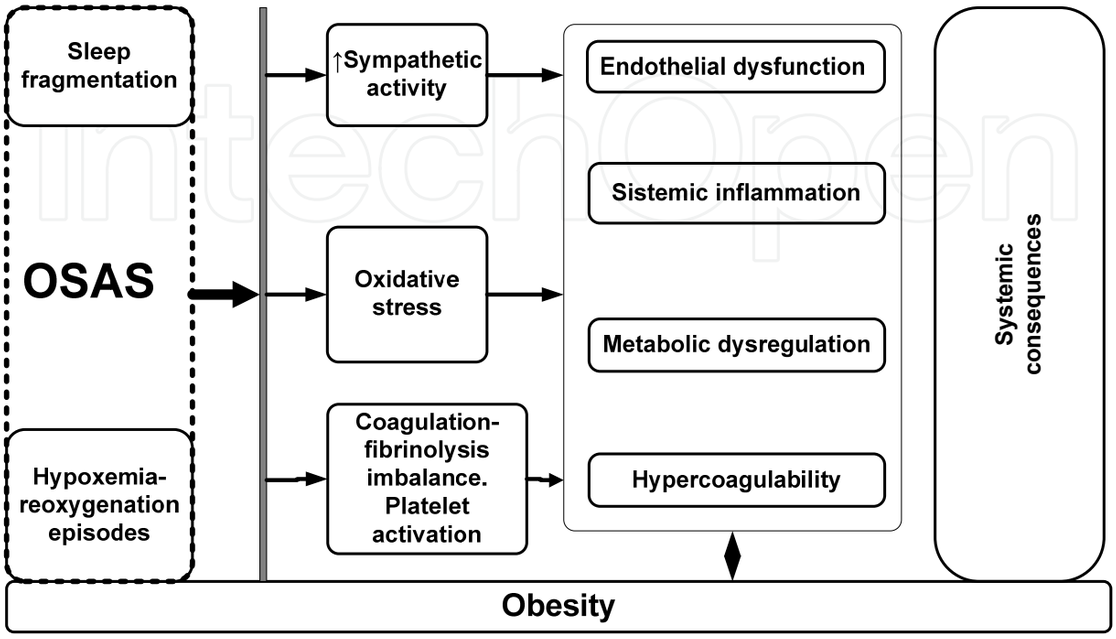


Fig. 1. A schematic summary of the proponed sequence of events in OSAS starting from episodic hypoxia and ending with systemic consequences.

Sleep fragmentation increases sympathetic nervous activity, which, in turn, results in a higher metabolic rate and elevated catecholamine secretion. Furthermore, severe sleep fragmentation can disturb nocturnal renin and aldosterone secretion profiles, and increase nighttime urine excretion. Moller et al. found that long-term CPAP reduced blood pressure, which was correlated with reductions in plasma renin and angiotensin II levels (Moller et al., 2003).

Although the mechanism of this altered inflammatory status in humans undergoing experimental sleep loss is unknown, it is likely that autonomic activation and metabolic changes play key roles (Mullington et al., 2010).

3. Enhanced sympathetic traffic

In OSAS patients, tonic activation of chemoreflex activity produces enhanced sympathetic traffic (Somers et al., 1988). Cyclic intermittent hypoxia (IH) and hypercapnia provides the causal link between upper airway obstruction during sleep and sympathetic activation during awakening. In a recent study in healthy humans, IH significantly increased sympathetic activity and daytime blood pressure after a single night of exposure. The baroreflex control of sympathetic outflow declined (Tamisier et al., 2011). Surges in sympathetic nervous system activity associated with apneic events have also been related to antifibrinolytic activity reflected by elevations in PAI-1 (von & Dimsdale, 2003). During

apneic events, there is an up-regulation of the renin-angiotensin system and down-regulation of nitric oxide synthases (Fletcher et al., 1999; Prabhakar et al., 2001).

The increased sympathetic activity and IH associated with apneic episodes has been proposed as a possible mechanism behind the association between OSAS, systemic inflammation and cardiovascular disease. CPAP reduces sympathetic nerve activity (Maser et al., 2008), increases arterial baroreflex sensitivity (Marrone et al., 2011) and decreases vascular risk (Kohler et al., 2008).

4. Oxidative stress

There is an emerging consensus that OSAS is an oxidative stress disorder. In a recent study involving children with OSAS, Malakasioti found an increase of hydrogen peroxide levels in exhaled breath condensate, which is an indirect index of altered redox status in the respiratory tract (Malakasioti et al., 2011).

Apnea produces a decline in oxygen levels followed by reoxygenation when breathing resumes. The cyclical episodes of hypoxia-reoxygenation, analogous to cardiac ischemia/reoxygenation injury causing ATP depletion and xanthine oxidase activation, and increases the generation of oxygen-derived free radicals. CPAP therapy decreases the levels of oxidative stress in OSAS patients (Chin et al., 2000; Alonso-Fernandez et al., 2009).

Oxidative stress can profoundly regulate the cellular transcriptome through activation of transcription factors, including specificity protein-1, hypoxia-inducible factor-1, c-jun, and possibly nuclear factor-kappaB. Activation of redox-sensitive gene expression is suggested by the increase in some protein products of these genes, including VEGF (Teramoto et al., 2003), EPO (Marrone et al., 2008), endothelin-1 (Belaidi et al., 2009), inflammatory cytokines and adhesion molecules (Ohga et al., 1999; Dyugovskaya et al., 2002; Ohga et al., 2003).

Increased oxidative stress has been associated with development of cardiovascular diseases and can be promoted by the chronic intermittent hypoxia characteristic of OSAS (Park et al., 2007). A variety of studies suggest that oxidative stress is present in OSAS at levels relevant to tissues such as the arterial wall (Grebe et al., 2006; Barcelo et al., 2006). This process enhances lipid uptake into human macrophages and may contribute to atherosclerosis in OSAS patients (Lattimore et al., 2005). Furthermore, OSAS decreases blood antioxidant status in high BMI subjects and may change the relationship between oxidative stress markers (Wysocka et al., 2008). After CPAP, expression of eNOS and phosphorylated eNOS was found to be significantly increased whereas expression of nitrotyrosine and nuclear factor-kappaB significantly decreased (Jelic et al., 2010) but some studies shown that CPAP may not affect antioxidant defense (Alzoghaibi & Bahammam, 2011).

Recently, Nair reported that oxidative stress is mediated, at least in part, by excessive NADPH oxidase activity. This author suggests that pharmacological agents targeting NADPH oxidase may provide a therapeutic strategy in OSAS (Nair et al., 2011).

5. Systemic inflammation

Local and systemic inflammation is present in OSAS. Insofar as local inflammation, bronchial and nasal changes are especially relevant (Devouassoux et al., 2007). In a recent study, patients

showed a significant increase in IL-8 and ICAM concentrations in both plasma and exhaled condensate. In addition, they showed a higher neutrophil percentage in induced sputum. These findings were significantly and positively correlated to AHI (Carpagnano et al., 2010), however, CPAP-therapy did have a significant effect (Lacedonia et al., 2011).

Several studies have reported changes in circulating levels of adhesion molecules in OSAS patients (El-Solh et al., 2002; Zamarron-Sanz et al., 2006). Dyugovskaya analysed polymorphonuclear apoptosis and expression of adhesion molecules in vitro in patients with moderate to severe OSAS. Decreased apoptosis and increased expression of adhesion molecules were observed. Although adhesion molecules may facilitate increased polymorphonuclear-endothelium interactions, decreased apoptosis may further augment these interactions and facilitate free radical and proteolytic enzymes (Dyugovskaya et al., 2008).

OSAS patients present increased levels of inflammatory mediators such as TNFα and IL-6 (Imagawa et al., 2004; Bravo et al., 2007) that decrease with CPAP treatment (Arias et al., 2008; Steiropoulos et al., 2009).

Systemic inflammation is increasingly being recognized as a risk factor for a number of complications including atherosclerosis (Ross, 1999) and is a well-established factor in the pathogenesis of cardiovascular disease (Hansson, 2005). Certain acute-phase proteins that have been associated in humans with cardiovascular disease, such as serum amyloid (Svatikova et al., 2003), C-reactive protein (Taheri et al., 2007; Punjabi & Beamer, 2007) which have been associated in humans with cardiovascular disease are elevated in OSAS patients and improve with CPAP treatment (Yokoe et al., 2003; Kuramoto et al., 2009).

The mechanisms by which inflammation contributes to OSAS-induced vascular dysfunction are not known. Reoxygenation after a brief period of hypoxia as experienced repetitively and systematically by OSAS patients may predispose to cell stress. It has been suggested that such events favor the activation of a proinflammatory response as mediated through the nuclear transcription factor nuclear factor-kappaB, a master regulator of inflammatory gene expression.

Inflammation may be an important link between increased sympathetic nervous system activity and vascular dysfunction in OSAS. Chronically elevated sympathetic activity produced an inflammatory response in several organs and vascular beds (Yu et al., 2005).

Some authors point to the role of the T-lymphocyte. This cell is known to play an important role in ANG II-induced hypertension and endothelial dysfunction via NADPH oxidase-induced superoxide production (Guzik et al., 2007).

Increased expression of inflammatory cytokines may contribute to endothelial dysfunction and subsequent cardiovascular complications (Ryan et al., 2005; Foster et al., 2007). Currently, some studies suggest that pentraxin 3, an acute phase response protein, is rapidly produced and released by several cell types, in particular by mononuclear phagocytes, and endothelial cells in response to primary inflammatory signals, may play a significant role in OSAS-associated vascular damage (Kasai et al., 2011). Arnaud report that some inhibition of molecules such as RANTES/CCL5, a cytokine that is a a selective attractant for memory T lymphocytes and monocytes may play a significant role in athesroscletoric remodeling OSAS-associated vascular damage (Arnaud et al., 2011)

However, mesenchymal stem cells triggered an early anti-inflammatory response in rats subjected to recurrent obstructive apneas, suggesting that these stem cells could play a role in the physiological response to counterbalance inflammation in OSAS (Carreras et al., 2010).

In a recent study on healthy human males, Querido et al. analysed the effect over 10 days of nightly IH in the following systemic inflammatory markers: serum granulocyte macrophage colony-stimulating factor, interferon-gamma, interleukin-1 β, interleukin-6, interleukin-8, leptin, monocyte chemotactic protein-1, vascular endothelial growth factor, intracellular adhesion molecule-1, and vascular cell adhesion molecule-1. There was no significant change in any of the markers. These findings suggest that a more substantial or a different pattern of hypoxemia might be necessary to activate systemic inflammation, that the system may need to be primed before hypoxic exposure, or that increases in inflammatory markers OSAS patients may be more related to other factors such as obesity or nocturnal arousal (Querido et al., 2011).

6. Hypercoagulability

Hypercoagulability resulting from increased coagulation or inhibited fibrinolysis is associated with an increased risk for cardiovascular disease (Zouaoui et al., 2006). This is another factor implicated in the association between this disease and OSAS (Peled et al., 2008).

A variety of findings support the existence of a relation between hypercoagulability, OSAS and cardiovascular disease. Firstly, patients with OSAS present higher plasma levels of several procoagulant factors such as fibrinogen (Reinhart et al., 2002; Tkacova et al., 2008), activated clotting factor FVII, FXIIa and thrombin/antithrombin III complexes (von et al., 2005) and the fibrinolysis-inhibiting enzyme plasminogen activator inihibitor (PAI-1) (von et al., 2006; Zamarron et al., 2008). Secondly, increased D-dimer levels in untreated OSAS have been correlated with severity of nocturnal hypoxemia, characteristic of OSAS (Shitrit et al., 2005). Thirdly, sleep fragmentation and sleep efficiency data have been associated with increased levels of von Willebrand factor and soluble tissue factor, two markers of a prothrombotic state (von et al., 2007).

OSAS is associated with platelet activation (Akinnusi et al., 2009). Platelet activation is a link in the pathophysiology of diseases prone to thrombosis and inflammation (Gasparyan et al., 2011). In these patients, platelet activation is associated with greater levels of oxygen desaturation (Oga et al., 2009;Rahangdale et al., 2011) that decreases after CPAP treatment (Varol et al., 2011).

In a current article, thromboelastography, a simple test of hemostasis, has been proposed for evaluating the risk of future cardiovascular disease in patients with OSAS (Othman et al., 2010).

7. Endothelial dysfunction

Endothelial dysfunction is an early marker of vascular abnormality preceding clinically overt cardiovascular disease (Giannotti & Landmesser, 2007; Halcox et al., 2009).

The intact endothelium regulates vascular tone and repair capacity, maintaining proinflammatory, anti-inflammatory, and coagulation homeostasis. Alteration of these

homeostatic pathways results in endothelial dysfunction before structural changes in the vasculature. The hypoxia, hypercapnia, and pressor surges accompanying obstructive apneic events may serve as potent stimuli for the release of vasoactive substances and for impairment of endothelial function.

In OSAS, endothelial dysfunction could be caused by both hypoxia-reoxygenation cycles and chronic sleep fragmentation produced by repetitive arousals. A causal relationship between OSAS and endothelial dysfunction was demonstrated by a study in which flow-mediated dilation in the forearm was improved by CPAP treatment (Ip et al., 2004; Trzepizur et al., 2009). Levels of nitric oxide, a major vasodilator substance released by the endothelium, have been found to be decreased in OSAS patients, and these levels normalize with CPAP therapy (Haight & Djupesland, 2003).

A number of studies with OSAS patients indicate an associated endothelial dysfunction (Nieto et al., 2004). In patients with OSAS, increased production of superoxide by neutrophils (Schulz et al., 2000), increased biomarkers of lipid peroxidation (Lavie et al., 2004), and increased levels of 8-isoprostanes (Alonso Fernandez 2009; Carpagnano et al., 2003) have been observed.

Among the most important vasoconstrictive substances is endothelin-1, a peptide hormone secreted under the influence of hypoxia (Kanagy et al., 2001). Several studies have reported higher endothelin-1 levels in OSAS patients (Phillips et al 1999; Saarelainen & Hasan, 2000) however, Grimpen reports conflicting findings (Grimpen et al., 2000). This divergence might be explained by differences in study design. The groups studied by Phillips (Phillips et al., 1999) and Saarelainen (Saarelainen & Hasan, 2000) had more severe disease and, thus, underwent more severe oxygen desaturations that acted as a trigger for endothelin-1 secretion. Gjorup showed that hypertensive OSAS patients had greater nocturnal and diurnal endothelin-1 plasma levels than healthy controls, suggesting that OSAS does not affect plasma endothelin-1 levels in the absence of coexistent cardiovascular diseases (Gjorup et al., 2007).

The inconsistency of the above endothelin-1 levels likely reflects the predominantly abluminal release of endothelin. Using rat models of arterial hypertension, several authors have reported elevated vascular production of endothelin-1, while circulating levels remained similar to controls (Pohl & Busse, 1989; Rossi & Pitter, 2006). This demonstrates that circulating levels of endothelin-1 do not exclude elevated vascular production in OSAS.

In recent years, endothelial progenitor cells have gained a central role in vascular regeneration and endothelial repair capacity through angiogenesis and restoring endothelial function of injured blood vessels. Endothelial progenitor cells are decreased in patients with endothelial dysfunction and underlie an increased risk for cardiovascular morbidity in OSAS. Endothelial progenitor cells may have a potential role in the pathogenesis of vascular diseases that is pertinent to OSAS (Berger & Lavie, 2011).

It has recently been reported that OSAS patients presented increased oxidant production in the microcirculation and endothelial dysfunction, both of which improved with treatment (Patt et al., 2010)

8. OSAS and endocrine-metabolic consequences

Even though OSAS is generally less prevalent in women than men, differences diminish after the onset of menopause. This may be the result of declining estrogen and progesterone

(Resta et al., 2004; Anttalainen et al., 2006). Accordingly, estrogen replacement therapy in menopausal women lessens the prevalence of OSAS (Shahar et al., 2003; Wesstrom et al., 2005).

On the other hand, men diagnosed with OSAS may manifest decreased libido and a decline in morning serum testosterone levels (Teloken et al., 2006; Hoekema et al., 2006). At first, this was thought to reflect an associated dysfunction of the pituitary-gonadal axis related to sleep fragmentation and hypoxia (Meston et al., 2003). However, the correction of hypoxia and sleep fragmentation in OSAS patients treated with CPAP does not lead to complete recovery, suggesting that existence of other underlying causes. In a recent study, with the exception of prolactine, CPAP therapy produced no significant changes the serum level of sexual hormones including FSH and LH (Macrea et al., 2010). Some authors claim that obesity is the major contributing factor to the reduced pituitary gonadal function in OSAS (Luboshitzky et al., 2005).

9. Obesity

Central, or visceral, obesity is associated with the greatest risk for OSAS (Shinohara et al., 1997). The mechanism by which obesity can favor the onset of OSAS is not well-known, but it could be that central obesity precipitates or exacerbates OSAS because fat deposits in the upper airway affect distensibility (Isono, 2009). The increased volume of abdominal fat could predispose to hypoventilation during sleep and/or reduce the oxygen reserve, favoring oxygen desaturation during sleep (Schwartz et al., 2008). In addition, the disrupted sleep patterns characteristic of OSAS predispose to metabolic effects and weight gain. Patel investigated the association between self-reported usual sleep duration and subsequent weight gain in the Nurses' Health Study. They showed that a habitual sleep time of less than 7 hours is associated with a modest increase in future weight gain and incident obesity (Patel et al., 2006).

In recent years, much attention has been focused on the interaction between OSAS and products released by adipose tissue such as leptin, adiponectin, resistin and grelin (Ronti et al., 2006).

Leptin is an adipocyte-derived hormone that regulates body weight through control of appetite and energy expenditure (Proulx et al., 2002). Furthermore, leptin is a cytokine and is therefore also involved in the inflammatory process. Several studies have shown increased levels of leptin in OSAS (Phillips et al., 2000; Tokuda et al., 2008), suggesting its role in the disease (Ip et al., 2000). The mechanisms underlying the relation between leptin and OSAS are very diverse, and may involve overnight changes in apnea levels (Patel et al., 2004; Sanner et al., 2004), sleep hypoxemia (Tatsumi et al., 2005), and hypercapnia (Shimura et al., 2005).

A direct relationship between OSAS and leptin is supported by the fact that effective OSAS treatment with CPAP also influences leptin levels (Shimizu et al., 2002; Cuhadaroglu et al., 2009). Although the precise mechanism explaining the effect of CPAP has not yet been elucidated, it can be inferred that reduction in sympathetic activity (Snitker et al., 1997), and improvement in insulin sensitivity play a role (Brooks et al., 1994).

Leptin levels have been proposed as a prognostic marker for OSAS (Ozturk et al., 2003) and have been implicated in the pathogenesis of OSAS-related cardiovascular disease (Kapsimalis et al., 2008; Tokuda et al., 2008; Al et al., 2009).

Leptin can also act as a respiratory stimulant, and impairment of the leptin signaling pathway causes respiratory depression in mice (O'Donnell et al., 2000). This hormone has been associated with obesity hypoventilation syndrome in humans (Phipps et al., 2002) and may reflect a compensatory response to hypoventilation (Makinodan et al., 2008).

OSAS has independently been associated with reduced levels of adiponectin (Masserini et al., 2006; Zhang et al., 2006; Carneiro et al., 2009) which may favour cardiovascular disease development. The recurrent hypoxia-reoxygenation attacks in OSAS patients may activate oxidative stress and lead to low levels of adiponectin (Vatansever et al., 2010).

Some authors have observed that serum adiponectin levels may be independent of the degree of OSAS (Tokuda et al., 2008). Decreased adiponectin may result from increased sympathetic activity (Delporte et al., 2002), and higher levels of cytokines such as IL-6 and TNFα (Fasshauer et al., 2003). In fact, there are conflicting reports as to whether CPAP treatment of OSAS effectively normalizes adiponectin levels (de Lima et al., 2010).

Obesity has been implicated in the relation between OSAS and adiponectin (Makino et al., 2006), In a recent study involving media under hypoxic conditions in an ex-vivo mouse model, adiponectin secretion was measured. In obese mice, hypoxic stress reduced adiponectin in the supernatant of mesenteric fat tissue, but not subcutaneous fat tissue. These findings suggest that abdominal obesity, representing abundant mesenteric fat tissue susceptible to hypoxic stress, partly explains adiponectin levels in OSAS patients, and that reduction of visceral fat accumulation may combat OSAS-related atherosclerotic cardiovascular diseases in abdominal obesity (Nakagawa et al., 2011).

Resistin is a white adipose tissue hormone whose function has yet to be established. In a study of 20 obese OSAS patients, Harsch found that CPAP treatment of OSAS had no significant influence on resistin levels (Harsch et al., 2004). In OSAS patients, hypoxic stress during sleep may enhance resistin production, possibly mediating systemic inflammatory processes. Through its effect on OSAS, CPAP therapy may help control resistin production (Yamamoto et al., 2008).

OSAS may decrease serum resistin levels in subjects with excess body mass and also may contribute to glucose metabolism, but has no influence on leptin levels (Wysocka et al., 2009)

Ghrelin is a hormone that influences appetite and fat accumulation and its physiological effects are opposite to those of leptin. No clear relation has been found between ghrelin and OSAS. In a study of 30 obese OSAS patients, Harsch found that plasma ghrelin levels were significantly higher in OSAS patients than in controls. These elevated ghrelin levels could not be explained by obesity alone, since they rapidly decreased with CPAP therapy (Harsch et al., 2003). In another study of 30 untreated obese patients with moderate-severe OSAS, significantly higher levels of serum leptin were found in OSAS patients than in controls, but ghrelin levels were no different (Ulukavak et al., 2005).

In a recent study of 55 consecutive OSAS patients, the study group presented significantly higher serum ghrelin levels than controls. There was a significant positive correlation

between ghrelin and AHI. No significant difference was noted in the levels of leptin, adiponectin, and resistin (Li et al., 2010).

Increased ghrelin levels have been found to support the presence of increased appetite and caloric intake in obese patients with OSAS, which in turn may further promote the severity of the underlying conditions (Spruyt et al., 2010). In obese children, OSAS is associated with daytime sleepiness, elevation of proinflammatory cytokines, increased leptin, and decreased adiponectin (Tsaoussoglou et al., 2010).

10. OSAS and insulin resistance

A variety of studies based on animal models indicate that hypoxia can alter glucose homeostasis (Cheng et al., 1997; Li et al., 2006). Polotsky described that long-term exposure to intermittent hypoxia increased levels of insulin and glucose intolerance in obese, leptin-deficient mice (Polotsky et al., 2003). Humans exposed to hypoxia present worsened glucose tolerance (Braun et al., 2001).

Insulin resistance is a central part of the metabolic syndrome, a condition that is reaching epidemic proportions in Western Society and now emerging in developing countries (Prentice, 2006). Most studies involving OSAS and insulin resistance demonstrate an association between these two diseases, independently of obesity (Tassone et al., 2003; McArdle et al., 2007). In a large population-based study involving normoglycemic hypertensive men, Resnick found that the severity of OSAS was associated with increased insulin resistance (Resnick et al., 2003). The magnitude of these beneficial effects is modulated by the hours of CPAP adherence and the degree of obesity (Tasali et al., 2011).

Insulin resistance is associated to states of inflammation (Reaven, 2005). Monocyte chemoattractant protein-1 levels are elevated in OSAS and may be involved in the pathogenesis of insulin resistance in these patients (Piemonti et al., 2003; Hayashi et al., 2006).

11. Metabolic syndrome and OSAS

Metabolic syndrome is an emerging public health problem that represents a constellation of cardiovascular risk factors (Batsis et al., 2007). The clinical identification of metabolic syndrome is based on measures of abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, and glucose intolerance (Executive Summary of the NCEP., 2001).

Although the etiology of this syndrome is largely unknown, it is likely to be comprised of a complex interaction between genetic, metabolic, and environmental factors (Nestel, 2003). Several recent studies suggest that a proinflammatory state may also be an important component (Aso et al., 2005; Gude et al., 2009). The close association between OSAS and metabolic syndrome is called "Syndrome Z"(Wilcox et al., 1998)

The prevalence of metabolic syndrome is markedly higher among OSAS patients. Ambrosetti et al. studied 89 consecutive OSAS patients and found metabolic syndrome in 53% of them (Ambrosetti et al., 2006). Another recent study found a prevalence of 68% (Drager et al., 2009). Obese OSAS patients may have an increased rate of metabolic syndrome and higher levels of serum lipids, fasting glucose, leptin and fibrinogen than obese subjects without OSAS. Thus,

clinicians should be encouraged to systematically evaluate the presence of metabolic abnormalities in OSAS and vice versa (Basoglu et al., 2011).

Both clinical and animal studies suggest that an independent relationship may exist between OSAS and hyperlipidemia. Hypoxic stress produced by OSAS potentially increases the risk of hyperlipidemia. In rodent models, hyperlipidemia can result from exposure to intermittent hypoxia (Li et al., 2005). In a sample of nearly 5,000 subjects from the Sleep Heart Health study, there was a positive association between OSAS severity and increased serum total cholesterol and triglycerides, as well as decreased serum HDL, in people under the age of 65 (Newman et al., 2001).

In a population-based sample of four hundred women aged 20-70 years the frequency of metabolic syndrome increased from 10.5% in women with AHI <5 to 57.1% in women with AHI ≥ 30. AHI and minimal saturation level remained significantly associated with metabolic syndrome also when adjusting for the waist-to-hip-ratio (Theorell-Haglow et al., 2011).

Both OSAS and metabolic syndrome may exert negative synergistic effects on the cardiovascular system through multiple mechanisms (Bonsignore & Zito, 2008; Levy et al., 2009).

Intermittent hypoxia, the hallmark feature of OSAS, leads to a preferential activation of inflammatory pathways. Oxidative stress, cardiovascular inflammation, endothelial dysfunction, and metabolic abnormalities in OSAS could accelerate atherogenesis (Quercioli et al., 2010). Further studies are required to determine the precise role of inflammation in the cardiovascular pathogenesis of OSAS, particularly its interaction with oxidative stress, obesity and metabolic dysfunction (Kent et al., 2011)

12. Conclusions

OSAS patients experience hypoxia–reoxygenation episodes, hypercapnia and arousal from sleep with modifications in the autonomic nervous system, oxidative stress and inflammation. OSAS is frequently associated to endocrine metabolic alterations and obesity.

Inflammatory processes play an important role in the pathogenesis of atherosclerosis and circulating levels of several inflammation markers have been associated with future cardiovascular risk. OSAS plays a mediating role between obesity and cardiovascular disease. Clinical and experimental data suggest a relationship between OSAS and adipose tissue pathophysiology which appears biologically plausible, however, further research is still needed. Multiple factors have been proposed to activate proinflammatory pathways in obesity, including generation of reactive oxygen species, and release of inflammatory cytokines potentially activated by OSAS-related hypoxic stress. All of this indicates that, more than a local abnormality, OSAS should be considered a systemic disease.

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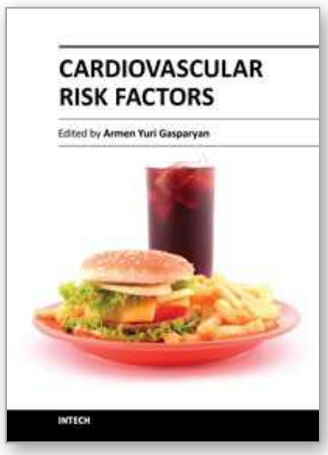
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Cardiovascular Risk Factors
Edited by Prof. Armen Gasparyan

ISBN 978-953-51-0240-3
Hard cover, 498 pages
Publisher InTech
Published online 14, March, 2012
Published in print edition March, 2012

Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

How to reference
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Carlos Zamarrón, Emilio Morete and Felix del Campo Matias (2012). Obstructive Sleep Apnoea Syndrome as a Systemic Low-Grade Inflammatory Disorder, Cardiovascular Risk Factors, Prof. Armen Gasparyan (Ed.), ISBN: 978-953-51-0240-3, InTech, Available from: http://www.intechopen.com/books/cardiovascular-risk-factors/obstructive-sleep-apnea-is-a-systemic-disease-

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