REVIEW
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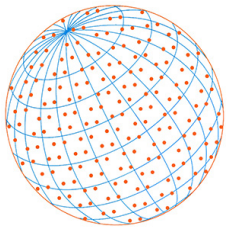

Aerosol and Air Quality Research

Air Pollution and Respiratory Permeability in Obstructive Sleep Apnea - A Review

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ABSTRACT

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent episodes of nocturnal upper airway obstruction during sleep, which can seriously affect sleep quality and cause sleepiness during the daytime. Known risk factors for OSA are numerous, including obesity, age, gender, craniofacial anatomy, smoking, alcohol consumption, and genetic inheritance. Recently, air pollution was linked to an increased risk of OSA severity. Alterations in permeability are considered to be an important factor in the development of OSA; however, the role of air pollution remains unclear. This review article explored the role of air pollution and airway permeability in the pathogenesis of OSA.

Keywords: Apnea Hypopnea Index, Nocturnal fluid shift, Obstructive sleep apnea, Particulate matter, Permeability

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1 INTRODUCTION

Economic burdens related to obstructive sleep apnea (OSA) account for billions of US dollars annually (AlGhanim *et al.*, 2008). Costs associated with OSA mostly arise from OSA diagnoses, treatments, and comorbidities (Kapur, 2010). Estimated costs for undiagnosed OSA range $34 billion to $69 billion annually (Knauert *et al.*, 2015). People with sleep disorders also work less efficiently than those without sleep difficulties (Sherman, 2013). In a population-based study of nearly 3000 subjects over 10 years, men with snoring and excessive daytime sleepiness were more than twice as likely to have occupation-related accidents (95% confidence interval (CI) = 1.3–3.8) (Lindberg *et al.*, 2001). It is also known that the quality of life (QOL) is lower in patients with severe OSA, and QOL substantially improves following clinical therapy such as continuous positive airway pressure (CPAP) (D'Ambrosio *et al.*, 1999; Akashiba *et al.*, 2002; Dutt *et al.*, 2013). Recently, there is emerging evidence of associations of environmental factors such as air pollution on increased risks of OSA; however, the underlying mechanisms of this relationship remain uncertain.

It was estimated that the prevalence of OSA ranged from 9% to 37% in men and from 4% to 50% in women (Franklin and Lindberg, 2015).

OSA is considered a multifactorial disease, including multiple genetic and environmental factors. Obesity is widely known as the most important risk factor for OSA. Older age, male

gender and smoking is also strongly associated with a higher risk for OSA. This current review focused on risk factors for OSA and possible mechanisms related to air pollution.

2 PREVALENCE OF OSA

OSA is a common disorder characterized by recurrent episodes of nocturnal upper airway obstruction associated with repeated cycles of desaturation and re-oxygenation, leading to sleep fragmentation and consequent daytime sleepiness (Senaratna *et al.*, 2017). OSA prevalence in adults more than 18 years of age, which is defined as a score of $\geq$5 on the Apnea Hypopnea Index (AHI), ranged from 9% (Reddy *et al.*, 2009) to 38% (Tufik *et al.*, 2010). Data from the Wisconsin Sleep Cohort showed that almost 25% men and nearly 10% in women of 30–60 years of age had OSA (Young *et al.*, 1993). In a cohort of more than 2000 subjects from Spain, an AHI of $\geq$ 5 was found in 26% of men and 28% of women (Duran *et al.*, 2001). A population-based study from Korea showed that the prevalence of OSA was more than one-fourth in men and 16% in women (Kim *et al.*, 2004). The estimated prevalence of OSA in Hong Kong was 8.8% for men and 3.7% for women (Ip *et al.*, 2001; Ip *et al.*, 2004), while the prevalence in India was 19.5% (Udwadia *et al.*, 2004). Interestingly, OSA occurs in roughly half of Swedish females aged 20–70 years old (Franklin *et al.*, 2013). When using the American Academy of Sleep Medicine (AASM) 2012 diagnostic criteria, it is postulated that almost 1 billion adults in the world have OSA. Therefore, OSA is an important public health issue worldwide.

3 RISK FACTORS FOR OSA

Risk factors for OSA are shown in Fig. 1.

3.1 Obesity

Obesity is regarded as one of the strongest risk factors for OSA (Franklin *et al.*, 2013). Since the obesity prevalence is growing globally (Punjabi, 2008; Garvey *et al.*, 2015), it is likely that the OSA prevalence is also increasing (Peppard *et al.*, 2013). A prospective cohort involving nearly 700 subjects found that a 10% increase in weight was associated with approximately a 33% increase in the AHI (Peppard *et al.*, 2000). It is believed that the volume of parapharyngeal fatty tissue is related to the severity of OSA (Shelton *et al.*, 1993). However, it is still controversial whether

Fig. 1. Risk factors of OSA.

neck or waist circumference is a better estimator of OSA compared to the body-mass index (BMI) alone (Young *et al.*, 2005). A cross-sectional study of 85 male subjects found that the AHI was correlated with abdominal fat (Schafer *et al.*, 2002). Nonetheless, data from the Sleep Heart Health Study showed that in addition to the BMI, neck circumference and waist circumference were also independent risk factors for severe OSA among middle-aged and older adults (Young *et al.*, 2002). In a prospective study of more than 50 patients, Ogretmenoglu *et al.* (2005) found that the BMI and body fat percentage (determined by a bioelectrical impedance assay) were correlated with the AHI.

Obesity may contribute to OSA through several mechanisms (Punjabi, 2008). Parapharyngeal fat can cause airway narrowing and collapse (Schwartz *et al.*, 2010). Leptin, a hormone produced by adipocytes and which is associated with the body composition, energy homeostasis and feeding behaviors, was significantly correlated with the AHI (Ulukavak Ciftci *et al.*, 2005). The relationship between leptin resistance and obesity was mentioned in a previous study (Carter *et al.*, 2013).

In a study of 18 subjects, patients with OSA had excess parapharyngeal fat deposition compared to non-OSA subjects as measured by the neck circumference (Mortimore *et al.*, 1998). Katz *et al.* (1990) found that the only contributors to the AHI were the external neck circumference, BMI, and pharyngeal internal circumference. Similarly, a Turkish cross-sectional analysis of 1912 subjects showed that the neck circumference was of greater value than the waist circumference in the association with OSA among men (Onat *et al.*, 2009).

3.2 Age

It was shown that an older age is associated with a higher OSA prevalence (Bixler *et al.*, 1998; Gabbay and Lavie, 2012). This can be explained by an increase in parapharyngeal fat and an elongated soft palate (Malhotra *et al.*, 2006). However, the OSA prevalence reaches a plateau after the age of 60 years (Bixler *et al.*, 1998; Young *et al.*, 2002), probably due to a smaller influence of BMI on elderly OSA subjects (Newman *et al.*, 2005). Another possibility is that elderly patients with OSA have a higher mortality than those without OSA.

3.3 Gender

It is known that the prevalence of OSA in men is 2–3-fold higher than in women (Punjabi, 2008; Gabbay and Lavie, 2012; Ralls and Grigg-Damberger, 2012). In the Sleep Heart Health Study over a 5-year follow-up, men were more likely to have an increase in the Respiratory Disturbance Index (RDI) than were women (Young *et al.*, 1993). This discrepancy may be explained by a sex difference in reporting symptoms of OSA, since women tend not to report common symptoms (loud snoring, cessation of breathing, and gasping), but instead report symptoms of fatigue and lack of energy (Young *et al.*, 1997). Furthermore, it is more likely for men to be referred to OSA specialists because of the expectation of physicians that OSA predominantly affects men. Sex hormones are also likely to be important in OSA, as the disorder is more common in post-menopausal women (Ralls and Grigg-Damberger, 2012). However, hormone replacement can reduce the severity of OSA in those patients (Shahar *et al.*, 2003; Wesstrom *et al.*, 2005).

3.4 Craniofacial Anatomy

It was shown that different craniofacial morphologies are correlated with OSA severity (Fan and Liu, 2010; Vidovic *et al.*, 2013; Fernandez-Salvador *et al.*, 2018; Sutherland *et al.*, 2018). For example, brachycephaly was a strong risk factor for high AHI scores in a white population (Cakirer *et al.*, 2001), while Chinese patients with OSA had retrognathia or micrognathia (Lam *et al.*, 2005). The mechanism for this phenomenon is that several craniofacial morphologies can change the airway shape and increase the likelihood of its collapse during sleep. Furthermore, tonsillar hypertrophy or an enlarged base of the tongue can also result in upper airway narrowing and cause OSA (Schwab, 2003).

3.5 Smoking and Alcohol

Current smoking, ex-smoking, and active and passive smoking are all strong factors for snoring and OSA (Khoo *et al.*, 2004; Quan *et al.*, 2014; Varol *et al.*, 2015; Bielicki *et al.*, 2019). Smoking

can result in OSA through airway narrowing, inflammation, and collapsibility during sleep (Pack *et al.*, 1992; Kim *et al.*, 2012). Alcohol consumption before sleep can also cause airway collapse and consequent OSA. Drinkers have an increased odds ratio (OR) of almost 1.33 times (95% CI; 1.10–1.62) for OSA compared to non-drinkers (Taveira *et al.*, 2018). However, the mechanisms for this collapse are still unclear. Experimental studies in animals (Bonora *et al.*, 1984) and humans (Krol *et al.*, 1984) showed that alcohol causes hypotonia of the oropharyngeal muscles by decreasing respiratory activity in the upper airway.

3.6 Genetic Inheritance

Several studies researched the role of genetic factors in the genesis of OSA. Segregation analyses showed that inherited factors can contribute to approximately 35% of the variance in OSA severity. Susceptibility loci for OSA were identified in genome-wide association scans (Patel *et al.*, 2012; Yin *et al.*, 2014; Zhang *et al.*, 2014; Gok *et al.*, 2015; Cade *et al.*, 2016), which showed an association of genetic loci and OSA in African-American and European-American subjects (Patel *et al.*, 2012).

3.7 Air Pollution

Air pollution is known to be an important risk factor for cardiopulmonary disease; however, few studies have investigated the effects of air pollution on OSA. In a study of over 3000 subjects from the Sleep Heart Health Study, an increased RDI and decreased sleep efficiency were associated with short-term augmentation in particulate matter (PM) of ≤ 10 μm in aerodynamic diameter (PM_{10}) and temperature in the summer (Zanobetti *et al.*, 2010). Another population-based study of nearly 2000 adults of 45–84 years of age in six cities of the USA from the Multi-Ethnic Study of Atherosclerosis showed that an increase in annual nitrogen dioxide (NO_2) and PM of $\leq$ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) was correlated with an increased OR of sleep apnea (Billings *et al.*, 2019). Specifically, each 5-μg m^{-3} per year increase in $PM_{2.5}$ led to a 60% higher OR of OSA. Similarly, a large population-based study of more than 4000 individuals in Taiwan also showed an association of 1-year $PM_{2.5}$ and NO_2 exposure with the AHI, which was greater during spring and winter (Shen *et al.*, 2018). In a retrospective study of more than 7000 subjects, the AHI was associated with atmospheric pressure and carbon monoxide (CO) exposure (Cassol *et al.*, 2012). Those authors found that OSA were more prevalent in winter than in other seasons. Interestingly, short-term elevated ozone (O_3) and temperature resulted in an increased AHI in a European study (Weinreich *et al.*, 2015). A study of more than 5000 subjects in Taiwan from 2008 to 2015 showed that PM_{10}, O_3, sulfur dioxide (SO_2), and humidity were only associated with severe OSA in the non-rapid eye movement sleep period (Cheng *et al.*, 2019).

4 ALTERATIONS IN THE PERMEABILITY OF AIRWAY BY PM

Several studies researched the relationship between a shift in body fluids and OSA in healthy people (Redolfi *et al.*, 2009), and in those with heart failure (Yumino *et al.*, 2010), hypertension (Friedman *et al.*, 2010), and renal failure (Elias *et al.*, 2012). The fact that non-obese patients wearing compression stockings during the day can decrease the AHI suggests a causative role of an overnight fluid shift in OSA (Silva *et al.*, 2017). A study of 36 subjects showed that patients with OSA had more baseline leg fluid than non-OSA patients, which suggests a greater fluid shift in OSA patients (Ding *et al.*, 2014). According to White, during the day, fluid is retained in the legs due to gravity. During night sleep, the fluid is redistributed to the neck also due to gravity, which leads to airway narrowing and consequent OSA (White and Bradley, 2013).

The mechanism for the rostral fluid shift can be explained by Starling's force. Patients with heart failure have high venous pressure, which results in more fluid being retained in the legs during the daytime. Consequently, when a patient lies down, more fluid in the legs will shift into the neck and cause OSA. Similarly, patients with a low protein state, which means low colloid osmotic pressure, will exhibit edema. However, edema also appears in healthy OSA patients, suggesting that OSA can lead to edema (Iftikhar *et al.*, 2008). The mechanism is still unclear and might be explained by an increase in the atrial natriuretic peptide (Kita *et al.*, 1998) and the activation of the renin-angiotensin-aldosterone system.

The association between airway permeability and air pollution was investigated in previous studies. High concentrations of diesel exhaust particles (DEPs) reduce occludin messenger RNA, which has an important role in maintaining the epithelial barrier integrity (Lehmann *et al.*, 2009). PM_{10} also reduces occludin expression and increases alveolar transepithelial electrical conductance (Caraballo *et al.*, 2011). Cadmium, a chemical element present in air pollutants, was shown to disrupt tight junction integrity (Cao *et al.*, 2015) *in vitro* via modulating genes associated with tight junctions. $PM_{2.5}$ also disrupts the nasal epithelial barrier via degradation of tight junction proteins (Zhao *et al.*, 2018). $PM_{2.5}$ is associated with Clara Cell Protein (CC16), a marker of epithelial barrier permeability (Timonen *et al.*, 2004; Jacquemin *et al.*, 2009) in adolescents (Provost *et al.*, 2014) and elderly men (Madsen *et al.*, 2008). Together, changes in permeability caused by air pollution could be an important pathophysiology of airway disease.

5 POSSIBLE MECHANISMS OF PM IN OSA

The mechanism of OSA by PM may be explained by oxidative stress and inflammation (Fig. 2). The composition of particles is very important for their toxicity. Thus, transition metals such as iron, copper, nickel, chromium, and vanadium can increase reactive oxygen species (ROS). Furthermore, volatile organic compounds (quinones and polycyclic aromatic hydrocarbons) in PM cause the production of ROS in neutrophils, eosinophils, macrophages, and bronchial epithelial cells. Normally, homeostasis in the body keeps oxidizing substances such as ROS and antioxidant defense mechanisms in a balanced state. However, when there are excess ROS generated during mitochondrial oxidative metabolism, oxidative stress occurs. This phenomenon leads to oxidative lipid degradation, protein oxidation, and consequent inflammation. $PM_{2.5}$ was reported to increase ROS in human nasal epithelial cells and decrease the viability of those cells (Hong *et al.*, 2016).

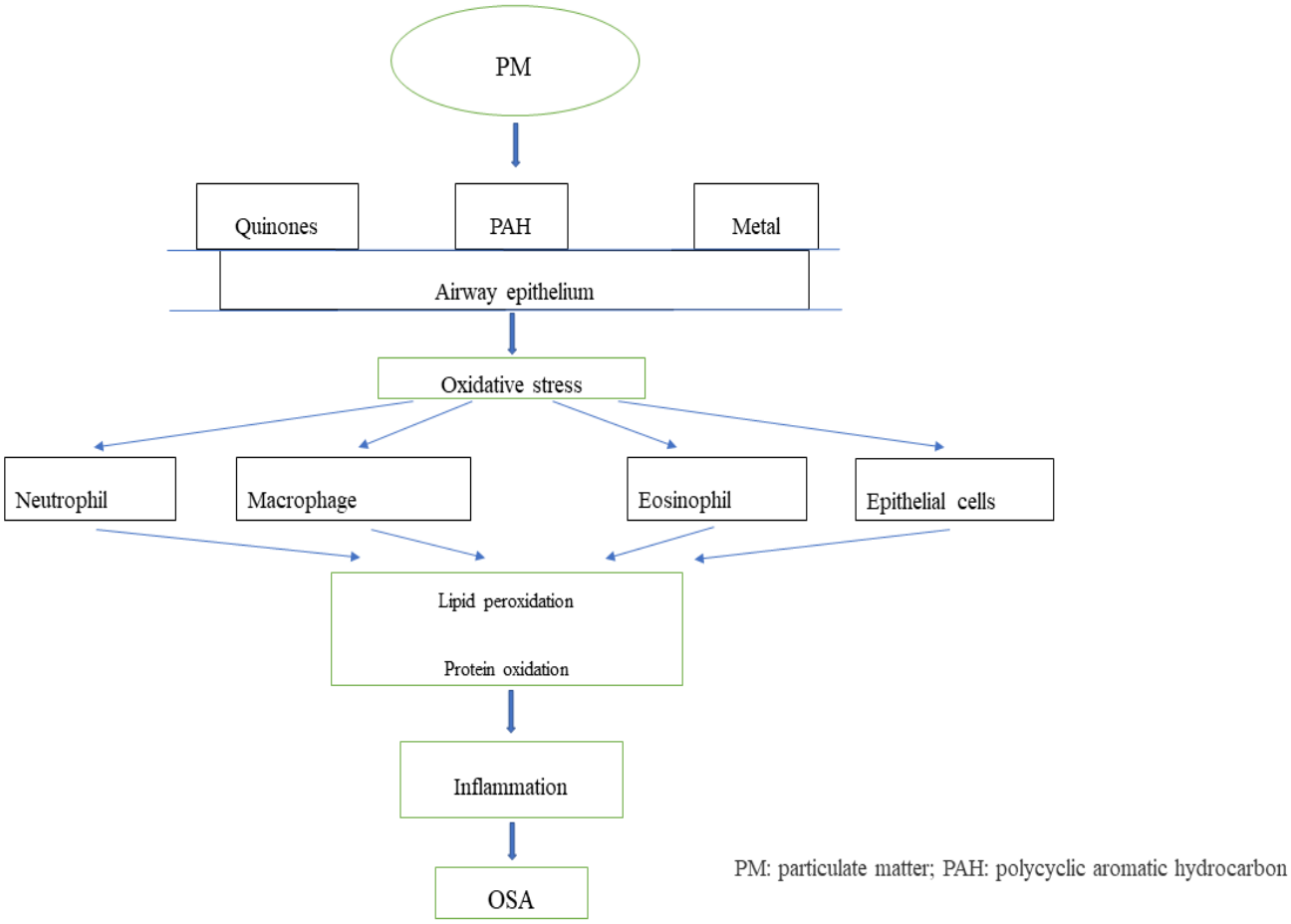

Fig. 2. The possible mechanisms of OSA by particulate matter.

PM-related oxidative stress and inflammation leads to hyperpermeability in the human upper airway and subsequent airway obstruction, thus causing OSA. Exposure to $PM_{2.5}$ also led to barrier disruption in the human epithelium by reducing expressions of tight junction proteins and increasing the secretion of inflammatory cytokines, which result in allergic rhinitis and rhinosinusitis (Zhao *et al.*, 2018; Kim *et al.*, 2019; Xian *et al.*, 2020). Furthermore, disruption of tight junctions by DEPs via a ROS-mediated pathway resulted in greater permeability of nasal epithelial cells and seasonal allergic rhinitis as observed in an animal model (Fukuoka *et al.*, 2016). $PM_{2.5}$ also caused hypersecretion in the rat airway (Harkema *et al.*, 2004). A study in China found a significant association of $PM_{2.5}$ and PM_{10} exposure with the prevalence of allergic rhinitis (Teng *et al.*, 2017).

6 CONCLUSIONS

This review paper demonstrates an association of air pollution and respiratory permeability in OSA**.** There is now considerable evidence that fluid accumulation in the legs during the daytime and the overnight fluid shift is a risk factor for OSA. Furthermore, airway permeability changes by air pollution play important roles in the pathogenesis of airway diseases. Further work is required to better understand patterns of fluid shifts in OSA and to completely elucidate the mechanisms of air pollution causing OSA.

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DISCLAIMER

The authors declare that they have no conflicts of interest.

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