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COMMENT

Obstructive sleep apnea without obesity: the beginning of a journey to "NOOSA"?

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While "Syndrome Z" is referred to as a combination of metabolic syndrome (MetS) with obstructive sleep apnea (OSA) [1], the prevalence of "Syndrome Z" in OSA ranges from 43% to 78% [2]. The prototype of MetS, a deadly quartet of hypertension, glucose intolerance, hypertriglyceridemia and central obesity, identified to predict cardiovascular risk [3]. On the other hand, OSA is defined as a sleep disorder breathing (SDB) characterized by recurrent narrowing or collapse of the pharyngeal airway during sleep despite continuous respiratory efforts [4], and is also a risk factor for cardiovascular disease [5]. Understanding the clustering of risk factors is clinically important to avoid underestimation of risk stratification.

A previous community-dwelling study has identified an obese phenotype with the burden of cardiometabolic risk factors. From the general population of Scotland and England [6], a total of 22,203 middle-aged men and women with no history of cardiovascular disease at baseline were followed for more than 7 yrs. Both non-obese and obese participants with two or more metabolic abnormalities were shown to have a significantly higher risk of cardiovascular disease compared with the metabolically healthy non-obese participants. In the Korean Genome and Epidemiology Study consisted of a total 140,137 participants, metabolically unhealthy participants had an increased risk of cardiovascular death in both non-obese and obese groups during a median follow-up of 9.2 yrs [7]. Although these results suggest that non-obese individuals with metabolic risks are also at risk for poor prognosis, there have been few studies on SDB and individual metabolic risk.

In the paper by Inoue et al., in this issue of the Journal, the cross-sectional relationship between SDB and hypertension was investigated with consideration for the effects of obesity in the Japanese occupational population [8]. Among total 2532 employees, 25% and 4% were classified into the moderate 3% oxygen desaturation index (ODI) group and high 3% ODI group, respectively. After adjusting for confounders, the odds ratio for hypertension increased significantly with higher 3%ODI levels, but further adjustment for obesity status of body mass index (BMI) ≥ 25 kg/m^2 attenuated that significant association. Stratified analysis by obesity status revealed that only non-obese subjects had a significant relationship between higher 3% ODI and hypertension. In addition to hypertension, the high 3%ODI group also had a higher prevalence of factors associated with glucose intolerance and lipid disorder. Considering patient demographics, OSA might account for a high proportion of SDB in the study reported by Inoue et al. [8].

Although the degree of obesity is lower in Asians than Caucasians, OSA is a common disease in both populations. Compared with Westerners, Asians also have a higher prevalence of increased nighttime blood pressure (BP) or morning BP surge, which may be partially due to OSA [9]. Even when a BMI cut off of 25 kg/m^2 was adopted, approximately two-thirds of non-obese patients with OSA (NOOSA) had hypertension and the half had impaired fasting glucose [10]. The high risk of MetS in NOOSA patients in the Indian population [10] suggests that non-obese individuals with a high 3% ODI are also at high risk for cardiovascular disease in the Japanese population [8].

Both in lean and obese individuals, presence of OSA was associated with significantly higher muscle sympathetic nerve activity than those found in non-OSA individuals [11].

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Higher sympathetic nervous system activity links in development of arterial hypertension and other metabolic risks. Metabolic dysfunction is also known to be present in lean OSA subjects [12]. In young lean men who are otherwise healthy and free of cardiometabolic disease, the presence of OSA was associated with insulin resistance and compensatory hyperinsulinemia [12]. Therefore, OSA is an upstream risk factor for MetS, and early intervention is expected to prevent MetS.

Intermittent hypoxia exacerbated cardiomyocyte hypertrophy and interstitial fibrosis. In the left ventricular (LV) myocardium, superoxide production, tumor necrosis factor α mRNA and 4-hydroxy-2-nonenal expression were increased with intermittent hypoxia in restricted-fed lean mice [13]. Adipose tissue inflammation, characterized by infiltration of macrophages and increased secretion of pro-inflammatory cytokines, was observed in lean chronic intermittent hypoxia rodent models and in isolated human adipocytes [14]. Whereas lean mice exposed to chronic intermittent hypoxia was found to exhibit visceral adipose tissue dysfunction via activation of hypoxia-inducible factor (HIF) and that increased expression of HIF-1α in that adipose tissue is associated with increased arterial BP and decreased insulin signaling and sensitivity [14]. Evidence from animal models of OSA has shown that chronic intermittent hypoxia induces fasting dyslipidemia even in lean mice [14]. Chronic frequent episodes of intermittent hypoxia and/or arousal response caused by OSA might contribute to the complication of LV hypertrophy in the long term.

Continuous positive airway pressure (CPAP) has been shown to have beneficial effects on individual components of MetS [15]. Generally, CPAP treatment for OSA has been shown to improve sleep apnea, especially excessive daytime sleepiness, and lower BP levels. An earlier Spanish study found that OSA was an independent risk factor for the development of LV diastolic dysfunction and that eliminating apnea with nasal CPAP improved LV diastolic dysfunction. Therefore, it has been proposed that chronic application of CPAP might avoid the development of LV diastolic abnormalities [16]. A meta-analysis of randomized controlled trials also supports the idea that CPAP may improve LV diastolic function in patients with OSA [17].

On the other hand, in the patients with non-sleepy OSA, CPAP therapy have no overall beneficial effects on subjective sleepiness, systolic BP, or cardiovascular risk compared with no active therapy [18]. OSA patients who were less sleepy had lower BMI and lower CPAP adherence. Thus, NOOSA patients might have lower CPAP adherence than obese patients with OSA (Fig. 1). Comprehensive management including an active lifestyle and regular support of CPAP use is key to managing this kind of OSA [18].

Sleep apnea in the absence of obesity is difficult to detect and is considered to have a poor prognosis, with a high possibility of concomitant MetS risks. Compliance with CPAP might be also poor, making it difficult to find an effective treatment. In the future, it will be necessary to understand its pathophysiology and consider effective intervention for NOOSA. In 1993, Reaven [19] proposed "Syndrome X" and wrote the following: "Throughout this presentation reference has been made to the fact that all of the elements of "Syndrome X" can be seen in non-obese individuals." and "All of clinical features of 'Syndrome X' can develop independently of obesity." Almost 30 years later, we cannot help but marvel at his foresight. This might be true of NOOSA with MetS risks. In that sense, the

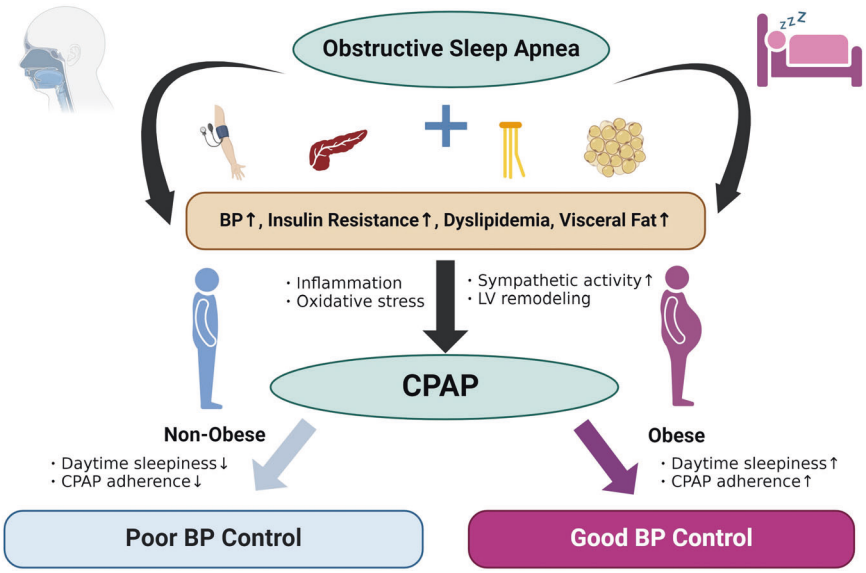

Fig. 1 Scheme for the relationship between obstructive sleep apnea and hypertension with and without obesity. BP bloodpressure, CPAP continuous positive airway pressure

findings of the study reported by Inoue et al. [8] have a chance of opening up a new field of research on NOOSA.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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