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REVIEW ARTICLE

Influence and implications of the renin–angiotensin–aldosterone system in obstructive sleep apnea: An updated systematic review and meta-analysis

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Summary

Obstructive sleep apnea is a chronic, sleep-related breathing disorder, which is an independent risk factor for cardiovascular disease. The renin–angiotensin–aldosterone system regulates salt and water homeostasis, blood pressure, and cardiovascular remodelling. Elevated aldosterone levels are associated with excess morbidity and mortality. We aimed to analyse the influence and implications of renin–angiotensin–aldosterone system derangement in individuals with and without obstructive sleep apnea. We pooled data from 20 relevant studies involving 2828 participants (1554 with obstructive sleep apnea, 1274 without obstructive sleep apnea). The study outcomes were the levels of renin–angiotensin–aldosterone system hormones, blood pressure and heart rate. Patients with obstructive sleep apnea had higher levels of plasma renin activity (pooled wmd+ 0.25 [95% confidence interval 0.04–0.46], $p = 0.0219$), plasma aldosterone (pooled wmd+ 30.79 [95% confidence interval 1.05–60.53], $p = 0.0424$), angiotensin II (pooled wmd+ 5.19 [95% confidence interval 3.11–7.27], $p < 0.001$), systolic (pooled wmd+ 5.87 [95% confidence interval 1.42–10.32], $p = 0.0098$) and diastolic (pooled wmd+ 3.40 [95% confidence interval 0.86–5.94], $p = 0.0086$) blood pressure, and heart rate (pooled wmd+ 3.83 [95% confidence interval 1.57–6.01], $p = 0.0009$) compared with those without obstructive sleep apnea. The elevation remained significant (except for renin levels) when studies involving patients with resistant hypertension were removed. Sub-group analysis demonstrated that levels of angiotensin II were significantly higher only among the Asian population with obstructive sleep apnea compared with those without obstructive sleep apnea. Body mass index accounted for less than 10% of

the between-study variance in elevation of the renin–angiotensin–aldosterone system parameters. Patients with obstructive sleep apnea have higher levels of renin–angiotensin–aldosterone system hormones, blood pressure and heart rate compared with those without obstructive sleep apnea, which remains significant even among patients without resistant hypertension.

KEYWORDS
aldosterone, angiotensin, obesity, renin–angiotensin–aldosterone system, sleep apnea, sleep disorder

1 | INTRODUCTION

The renin–angiotensin–aldosterone system (RAAS) comprises of three major hormones—renin, angiotensin II (AngII) and aldosterone. Aldosterone, the key hormone in the mineralocorticoid pathway, plays a fundamental role in salt and water homeostasis, blood pressure regulation, and cardiovascular remodelling. Elevated aldosterone levels are shown to be associated with cardiovascular and renal injuries contributing to the excess morbidity and mortality (Funder, 2017). For decades, it was believed that the activation of RAAS, mainly in response to intravascular volume contraction, regulated the biosynthesis of aldosterone (Brown, 2008; Cooper et al., 2007). In the RAAS, renin converts angiotensin into angiotensin I (AngI), which in turn is converted to AngII by angiotensin-converting enzyme (ACE). ACE is found primarily in the vascular endothelium of the lungs and kidneys. AngII acts on the proximal convoluted tubule of the kidney, increasing sodium reabsorption, which subsequently increases blood pressure of the patient. AngII also acts on the adrenal cortex, specifically the zona glomerulosa, to stimulate release of aldosterone. There is growing evidence suggesting that aldosterone secretion is not solely under RAAS regulation. Increased levels of plasma and urinary aldosterone have been demonstrated in people with obesity (Andronico et al., 2001; Goodfriend et al., 1999; Mule et al., 2008; Rocchini et al., 1986).

Obstructive sleep apnea (OSA) and resistant hypertension are common in people with obesity (Martinez-Garcia et al., 2018). The prevalence differs with age and gender, being more common in males and with increasing age. It is a chronic, sleep-related breathing disorder, characterized by periodic narrowing and obstruction of the pharyngeal airway during sleep (Rundo, 2019). The American Academy of Sleep Medicine (AASM) categorizes OSA based on patients' apnea–hypopnea index (AHI): no OSA/normal for AHI < 5; mild OSA for AHI 5 ≤ 15; moderate OSA for AHI 15 ≤ 30; and severe OSA for AHI > 30. Apnea refers to the absence of breathing, while hypopnea refers to the reduction in airflow, both lasting at least 10 s, leading to abrupt oxygen desaturation during sleep. In response to the lack of oxygen, the brain alerts the body, causing a brief arousal from sleep in order to restore normal breathing. The fragmentation of sleep cycles is a physiological stress, leading to morbidities and mortalities. It is, thus, not surprising that OSA has been identified as an independent risk factor for cardiovascular disease (Marin et al., 2005; Redline & Foody, 2011) and a predictor of cardiovascular outcomes (Gami et al., 2013).

The relationship between OSA and hyperaldosteronism is less studied, with equivocal data (Prejbisz et al., 2017). Aldosterone levels contributed to the severity of OSA in patients with primary aldosteronism (PA) and resistant hypertension (Buffolo et al., 2019; Prejbisz et al., 2017). In a limited number of studies, PA was found to be more frequent in patients with OSA (Karcz et al., 2017). Similarly, patients with OSA demonstrated higher aldosterone levels and prevalence of PA (Prejbisz et al., 2013). The link between aldosterone and OSA could be bi-directional. It is hypothesized that aldosterone causes salt and water retention leading to oedema of the para-pharyngeal tissues, resulting in obstruction of the upper airway and worsening of OSA symptoms (Pimenta et al., 2009). Recurring upper airway collapse in OSA also causes intermittent hypoxia, which increases plasma levels of both renin and aldosterone in animal models, and stimulation of the chemoreceptor in the carotid body in rats (Iturriaga et al., 2016).

Given that both hyperaldosteronism and OSA lead to higher cardiovascular morbidity and mortality, we aimed to systematically review the literature and further elucidate and estimate the degree of derangement in the RAAS between individuals with and without OSA.

2 | MATERIALS AND METHODS

2.1 | Data sources and extraction

We performed a systematic search of all English-language medical literature published from inception till March 2021 using PubMed, CINAHL and Cochrane using the following MESH headings: "sleep apnea", "sleep-disordered breathing", "OSA", "OSAS", "OSAHS", "aldosterone", "primary aldosteronism", "renin-angiotensin aldosterone system" and "RAAS". We also looked into references of the selected papers. When the full texts were not available or when the reporting was inadequate, we attempted to contact the respective authors via email to obtain the full paper and more detailed data. Review articles, posters, abstracts and theses were excluded.

To be included in the analysis, studies had to fulfil the following criteria: (i) the diagnosis of OSA has been confirmed using standard diagnostic tools; (ii) comparison of aldosterone level or other surrogate parameters of RAAS between individuals with and without OSA