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Diuretics in Patients with Obstructive Sleep Apnea and Concomitant Hypertension

To the Editor:

We read with great interest the original article from Giatti and colleagues (1) exploring the relationship between dietary sodium intake and severity of obstructive sleep apnea (OSA) (1). These findings suggest that the role of dietary sodium in the pathogenesis of OSA cannot be generalized but rather is limited to hypertensive patients (2). We agree with the authors about the fact that fluid redistribution from the legs to the neck during sleep (i.e., fluid shift) contributes to the severity of OSA in the restricted population of patients with hypertension and may constitute a specific endotype and a potential therapeutic target.

We have recently published a propensity score-matched analysis addressing this issue in a huge national real-life prospective observational cohort of patients with OSA (3). The 69,564 included patients with OSA had a median age of 56.9 years (interquartile range: 47.4–65.6), 67% were men, and the median apnea–hypopnea index (AHI) was 28 (14–43) events/h. Among them, 9,783 (14.1%) were treated with diuretics. Severe OSA was defined as an AHI > 30 events/h, and the impact of diuretics on OSA severity was assessed by using a logistic regression model. We showed that diuretics reduce the severity of OSA only in patients with hypertension ($P < 0.01$) and particularly in patients with a body mass index (BMI) between 25 and 35 kg/m² ($P < 0.01$). No association was found between diuretics and OSA severity when we considered the entire population or subgroups suffering from heart failure (whatever their BMI), suggesting that this physiopathological trait is of lesser impact in this situation.

Many drugs have been investigated in randomized trials as candidate therapeutic agents for the management of OSA related to specific endotypes (e.g., poor upper airway muscle activity, high loop gain, low arousal threshold) (4). These research data do not currently translate into routine practice, and there are no clear recommendations for medications as primary therapy for OSA. The prevalence of hypertension in patients with OSA consistently reaches 50% across studies with a high rate of uncontrolled and resistant hypertension (5). According to our results, which are consistent with those of Giatti and

colleagues, diuretics may have the potential to both reduce OSA severity and treat OSA-related hypertension.

For primary hypertension, the main drug classes recommended for treatment initiation in monotherapy in all international guidelines are thiazide diuretics, β -blockers, long-acting calcium channel blockers, and renin–angiotensin blockers. In the general population, each of these therapeutic classes is considered equally effective. In view of our analysis and the existing literature, diuretics might be the first choice medication for patients with OSA with concomitant hypertension.

In addition, interventions to reduce bodily fluid content (e.g., low sodium intake or diuretics) in men with severe OSA have been shown to slightly decrease AHI, suggesting that rostral fluid displacement is one among other mechanisms determining pharyngeal collapsibility (6) and in turn OSA severity. A major goal for personalized and precision medicine is to combine therapies appropriate for specific well-defined OSA endotypes and phenotypes. Combinations of therapies can include continuous positive airway pressure (the gold standard therapy for OSA), lifestyle interventions (weight loss, low-salt diet, and/or exercise), and pharmacological interventions targeting OSA-related conditions. Further studies are needed to identify the role of diuretics in the distinct pathophysiological and clinical scenario of overweight or patients who are moderately obese with OSA and hypertension. ■

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Salt, Diuretics, and Obstructive Sleep Apnea

To the Editor:

We read with great interest the article by Giatti and colleagues, which was published recently in *AnnalsATS* (1). The authors aimed to investigate a possible involvement of sodium intake in obstructive sleep apnea (OSA) and found a significant association between sodium excretion level and OSA but only in hypertensive individuals. The most important issue to consider when interpreting the results was that the authors analyzed sodium excretion levels during the night (between 7 P.M. and 7 A.M.).

The relationship between blood pressure (BP) and diurnal variation in urinary sodium excretion has already been reported (2). BP was positively associated with nocturnal sodium excretion levels; however, no significant association was observed with BP during daytime. Therefore, in a separate analysis by BP level, hypertensive individuals excreted larger amounts of sodium during nighttime than normotensive individuals, whereas daytime excretion level was higher in normotensives (2). Higher urinary sodium excretion rate in hypertensive individuals was also observed in other studies (3, 4). Given the differences in diurnal rhythm of sodium excretion between normotensive and hypertensive individuals, it is difficult to estimate dietary salt intake per day from nighttime sodium excretion level alone, especially in hypertensive individuals.

Salt sensitivity of BP is present in some members of the population, wherein BP exhibits changes parallel to changes in salt intake (5). Salt sensitivity is a pathophysiology of increased nocturnal sodium excretion in hypertensive, or salt-sensitive, individuals. They are likely to have diminished renal sodium excretory capability and require longer time for natriuresis than non-salt-sensitive hypertensive or normotensive individuals, which results in carrying pressure natriuresis over into the night (6). This is evident from the results of an experimental epidemiological study, which showed that salt-sensitive essential hypertensive individuals had higher nocturnal BP to enhance pressure natriuresis during the night, and nocturnal BP of salt-sensitive hypertensive individuals, but not of non-salt-sensitive hypertensive individuals, further increased via salt loading during daytime (7). An involvement of salt sensitivity was also evident from the results that show that salt restriction normalizes not only daytime

but also nighttime BP in essential hypertensive patients with salt sensitivity (8).

Regarding the relationship between OSA and nocturnal sodium excretion, it has been reported that the apnea-hypoxia index was positively correlated with sodium excretion during the nighttime but not during the day (5). A plausible mechanism by which OSA increases natriuresis during the night is increased intrathoracic pressure and consequent larger venous return to the atrium, which in turn enhances natriuretic peptide secretion from the atrium (9). A close positive association between the 3% oxygen desaturation index and nocturnal urination frequency was also found in our observational study in the general population (10), which is in accordance with the pathophysiology of larger sodium excretion during the night in individuals with OSA.

Given these research findings, it is possible that coexistence of hypertension and OSA synergistically increases nighttime, but not daytime, sodium excretion levels, which supports Giatti and colleagues' findings, namely that sodium excretion during the night is associated with OSA but only in hypertensive participants. As described by the authors, fluid retention during the day and its shift into the neck by lying down at night, which causes upper airway narrowing via increasing tissue pressure, may be another reason for the association between excessive salt intake and consequent body fluid retention and OSA. However, to clarify whether high salt intake or sodium itself increases the risk of OSA, further studies comparing differences between daytime and nighttime sodium excretion and their relationship with OSA are required. ■


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