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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. ■

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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## Reply: Salt, Diuretics, and Obstructive Sleep Apnea

*From the Authors*:

We fully appreciated the interest in discussing our recent findings pointing to an independent association of sodium excretion with obstructive sleep apnea (OSA) in participants with hypertension but not in the normotensive ones (1). Until recently, it was not clear whether we could extrapolate the role of dietary sodium and related fluid retention on the OSA pathogenesis to all myriad of patients with this important and prevalent sleep-disordered breathing. The main take-home message from our study is that the role of sodium and related fluid retention is probably limited to hypervolemic conditions (1).

Drs. Tabara and Chin (2) appropriately argued that our strategy for limiting the sodium excretion analysis to 12 hours (7 P.M. to 7 A.M.) is not ideal, to which we agree. This strategy was chosen to minimize the inaccuracy of the urine volume collected and stored during working periods and to avoid the influence of significant sodium loss in sweat in this large sample size (1). As discussed in the paper, the ELSA-Brasil study previously validated the 12-hour urine collected at night to estimate 24-hour excretion of sodium (3, 4). Moreover, it is also important to stress that the 12-hour urine sample certainly surpasses the sleep time. Most of the participants from the ELSA-Brasil study slept 6–7 hours (5). In our study, we had the opportunity to perform additional analysis using 24h sodium intake instead of sodium excretion. The consistent results reinforce the main study message (1).

Despite these arguments, we agree that additional analysis using daytime and nighttime sodium excretion may provide incremental findings for improving our current understanding of sodium's impact on OSA according to the hypertension and blood pressure dipping status.

The influence of the individual susceptibility to the effects of salt intake (salt sensitivity) is another interesting point discussed by Tabara and Chin. Salt-sensitive individuals usually present an abnormal kidney reaction to salt intake (6) and have been estimated to be present in approximately half of the patients with hypertension and a quarter of normotensives (7); in this scenario, it is conceivable that salt-sensitive patients may be more susceptible to the fluid retention and therefore more susceptible to the upper airway collapse during sleep. The major challenge for pursuing this hypothesis is the lack of feasible and straightforward methods for measuring salt sensitivity in clinical practice due to multiple confounders (6).

We also are grateful for the comments provided by Revol and colleagues (8). They highlighted the potential role of diuretics on ameliorating OSA severity based on the overnight rostral fluid shift phenomenon. Their huge propensity-matched analysis data showed that the presence of diuretics reduced the severity of OSA only in patients with hypertension but not in the entire population (9). Our results are, therefore, in line with this real-life observation. The authors argued that these combined properties—a well-established antihypertensive treatment (10) and the effects on chronic fluid retention as a mediator of OSA severity—make diuretics one of the preferable choices for hypertensive patients with comorbid OSA. Although we agreed about this attractive strategy, definitive evidence from head-to-head comparisons between diuretics and other classes would be ideal. It is important to note, however, that the vast majority of available studies showed modest effects of diuretics on OSA severity (11, 12), underscoring the need for combined and personalized treatments as suggested by Revol and colleagues (8). ■



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