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Who May Benefit from Diuretics in OSA? A Propensity Score-Match Observational Study

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Abstract (247/250 words)

Background: Diuretics have been reported as effective for reducing obstructive sleep apnea (OSA) severity by preventing fluid retention and reducing rostral fluid shift. The benefit of diuretics might vary depending upon the OSA clinical phenotype and comorbidities. To test this hypothesis, we conducted a propensity score-matched cohort analysis of data from the French national sleep apnea registry “Observatoire Sommeil de la Fédération de Pneumologie” (OSFP).

Methods: A propensity score analysis was used to determine the impact of diuretics on OSA severity. Matching (ratio 1:4) was performed by using a 0.1 collider for the propensity score. Severe OSA was defined as an apnea-hypopnea index (AHI) > 30 events/h and the usefulness of diuretics was assessed using a logistic regression model.

Results: The 69,564 OSA patients studied in the OSFP prospective observational cohort had a median age of 56.9 years [Interquartile range (IQR): 47.4; 65.6], 67% were men, and the median AHI was 28 [14; 43] events/h. Among them, 9,783 (14.1%) were treated with diuretics. Diuretics reduced OSA severity in overweight or moderately obese patients ($p=0.03$) and in patients with hypertension ($p<0.01$), particularly in hypertensives with a body mass index between 25 and 35 kg/m² ($p<0.01$). Diuretics had no significant effect on OSA severity in patients with self-reported low physical activity or heart failure.

Conclusions: Diuretics appear to have a positive impact on OSA severity in overweight or moderately obese patients with hypertension. A prospective study is needed to confirm that diuretics are of interest in combined therapies for hypertensive patients with OSA.

Abbreviations

AHI apnea-hypopnea index

BMI body mass index

BP blood pressure

CPAP continuous positive airway pressure

ESS Epworth sleepiness scale

IQR interquartile range

ODI oxygen desaturation index

OSA obstructive sleep apnea

OSFP Observatoire Sommeil de la Fédération de Pneumologie [Sleep registry of the French
Pneumology Federation]

SD standardized difference

Introduction

Obstructive sleep apnea (OSA), one of the most frequent chronic diseases, is characterized by complete (apnea) or incomplete (hypopnea) collapse of the upper airway during sleep.¹ OSA is associated with excessive daytime sleepiness and an increased risk of cardiovascular and metabolic comorbidities.² Diverse and interrelated pathophysiological mechanisms include compromised pharyngeal anatomy (adipose tissue deposition, local inflammation, rostral fluid shift/edema), inadequacy of the upper airway muscles to stiffen/dilate the airway and maintain its patency in response to an increase in ventilatory drive, and finally, loss of efficacy of protective upper airway reflexes.² Among them, overnight fluid shift, from the legs to the upper body, produces a significant reduction in pharyngeal size, and increases pharyngeal resistance and upper airway collapsibility (See review by Perger *et al.*).⁵

Many drugs have been investigated in randomized trials as possible therapeutic agents for the management of OSA.^{4,6} These drugs might stimulate respiratory drive, reduce upper airway collapsibility or improve nasal patency.^{4,6-8} Diuretics could reduce pharyngeal edema contributing to sleep-disordered breathing in subpopulations of severe OSA patients. In a case series diuretics significantly decreased blood pressure (BP) and the apnea-hypopnea index (AHI) in 15 obese patients with hypertension and diastolic heart failure.⁹ Other studies also reported an improvement of OSA with diuretics in specific populations of uncontrolled or resistant hypertension.¹⁰⁻¹² These studies are interesting but partly flawed by their very small sample sizes and lack of account for confounders such as age, body mass index, other comorbidities, and physical activity levels.

A major goal for personalized and precision medicine in the OSA field is to combine therapies appropriate for specific well defined OSA phenotypes.^{13,14} Combinations of therapies can include continuous positive airway pressure (CPAP) the gold standard therapy

for OSA, life-style interventions (weight loss and exercise), and pharmacological interventions targeting OSA-related conditions.¹⁵

We hypothesized that the impact of diuretics on OSA severity would depend on the clinical phenotype and comorbidities. To address this question and properly account for confounders we conducted a propensity score-matched cohort analysis, using data from the French national sleep apnea registry “Observatoire Sommeil de la Fédération de Pneumologie” (OSFP, www.osfp.fr).

Materials and Methods

Study design and setting: the OSFP national registry

Data from the prospective national OSFP cohort were used to conduct this study. The OSFP registry¹⁴ is a standardized web-based reporting system administered by the French Federation of Pulmonology. It contains anonymized longitudinal data from patients complaining of sleep disorders who have been investigated by respiratory physicians in private practice, general hospitals and university hospitals. Periodic quality control checks are performed to ensure up-to-standard data-recording. Ethical committee approval for setting up the database was obtained from “Le Comité consultatif sur le traitement de l’information en matière de recherche en santé” (CCTIRS n° 09.521) and authorization from the “Commission Nationale Informatique et Liberté” (CNIL), the French information technology and personal data protection authority. The OSFP’s Independent Scientific Advisory Committee approved data use for this study. All patients included in the database provided written informed consent.

Population and data

Patients aged at least 18 years at their first medical visit were included in the study. All patients reported sleep complaints or a suspicion of OSA. During this visit, each patient was evaluated through a structured interview allowing the physician to complete an electronic medical record. All information was self-reported by the patient and validated by the physician. Even though no severity grade was used, sedentariness was confirmed by the clinician, based on the patient's description of his or her physical activity. The patient was then assessed by respiratory polygraphy or polysomnography to confirm the diagnosis of OSA.

The following data were collected at the first medical visit: demographic characteristics, medical history and co-morbidities (cardiovascular, metabolic and respiratory) and OSA/sleep disorder related symptoms. The control group included OSA patients without diuretics or patients with no treatment reported.

Statistical methods

Details of population characteristics are given using number and percentage for qualitative variables and median and interquartile range for quantitative variables. Comparisons between the groups (diuretics vs. no diuretics) were performed using a Chi² or Fisher exact test for qualitative variables and a non-parametric Mann-Whitney test for quantitative variables.

A propensity score method was used to account for confounders. Briefly, a logistic regression model was used to compute the propensity score, which is the probability, for a patient, of being treated with a diuretic. The variables introduced in this logistic regression model were selected in accordance with rules for propensity score matching (variable

associated either with outcome and exposure or with outcome only) (Table S1 in Supplemental materials).^{16,17} A 1:4 'greedy' matching procedure (one patient with diuretic matched with four patients without diuretics) was performed using a collider of 0.1 for the propensity score (Table S2 in Supplemental materials). This approach presents the advantage of being simple to use and has good performance.¹⁸ Due to the large sample size, 1:2 matching was also performed for sensitivity analysis. Standardized differences (SD) were computed for all variables after the propensity score matching. Results of the logistic regression model for the propensity score and standardized differences are presented in the Supplemental materials (Figure S1). Finally, a second logistic regression model was used to assess the impact of a diuretic on the probability of having severe OSA (defined as an AHI > 30 events/hour). Factors with a standardized difference greater than 10% after matching were introduced into the final model. Sensitivity analyses were performed by using different adjustments for the final model (propensity score only and adjustment on all ongoing variables used in the propensity score model).

Sub-group analyses were performed considering sedentariness, body mass index (BMI), heart failure, hypertension, and sub-groups by BMI categories for heart failure and hypertension. A 1:n matching procedure was performed for each sub-group analysis. SAS v9.4 (SAS Institute, Inc., Cary, North Carolina) was used for statistical analyses. A p-value of < 0.05 was considered as significant.

In addition, several matching methods were tested to ensure the robustness of the results: different calipers for greedy matching, stratification and optimal matching (see details in Supplemental materials).

Results

As shown in the study flow-chart (Figure 1), the overall population extracted in June 2019 included 101,791 patients. Among them, 69,564 exhibited OSA, with an AHI or oxygen desaturation index (ODI) > 5 events/hour. The number of patients on diuretic treatment at the time of OSA diagnosis was 9,783 (14.1%).

Characteristics of the OSA population

Characteristics of the 69,564 OSA patients are shown in Table 1. In the studied population, OSA patients had a median age of 56.9 years [Interquartile range (IQR): 47.4; 65.6], 67% were men, with a median AHI of 28 [14; 43] events/h. The median Epworth sleepiness scale (ESS) score was 10 [6; 13]. The matched population consisted of 42,565 patients, including 8,513 with diuretics (20%, matching ratio: 1:4), (Table S2 in Supplemental materials).

Effect of diuretics on OSA severity

The impact of diuretics on AHI in the whole population as well as in clinical subtypes of OSA (patients suffering from hypertension or heart failure) is reported in Figure 2. We found that ongoing diuretic treatment had no overall association with OSA severity when we considered the entire population. There was no association between diuretics and OSA severity in patients with heart failure (whatever their BMI) or sedentariness.

However, diuretics were associated with a reduction in the probability of exhibiting severe OSA in overweight or moderately obese patients ($25 < \text{BMI} < 35 \text{ kg/m}^2$). We also found a significant effect of diuretics on OSA severity in patients with hypertension. By considering different levels of BMI, this effect was significant for overweight or moderately obese patients (OR = 0.81 95%CI: [0.71; 0.92], $p < 0.01$ for BMI [25; 30] and OR = 0.83 95%CI: [0.73;

0.95], $p < 0.01$ for BMI [30; 35]). For patients without heart failure or hypertension (N = 2,174), there was no effect of diuretics on OSA severity (OR = 1.07 95%CI: [0.97; 1.18], $p = 0.15$). As reported in the Supplemental materials, the same results were obtained using 1:2 matching (Figure S3) or different propensity score matching methods (Table S4).

Discussion

Our results obtained from a propensity score-matched analysis in a very large prospective observational cohort (N = 69,564) with real life recruitment of OSA patients, confirm, expand and clarify previous data. In a series of 15 obese patients with hypertension and diastolic heart failure, intensive treatment with diuretics (intravenous administration of furosemide + spironolactone for 3 days) significantly decreased body weight, BP and AHI.⁹ Our results showed that the beneficial effect of diuretics is real for overweight or moderately obese OSA patients with hypertension but was not confirmed for patients with heart failure. The specific and additional benefit of diuretics may be more difficult to highlight in this subgroup of probably more severe patients with more confounders. Our results confirm three previous studies reporting an improvement of OSA in hypertensive patients treated by diuretics. Gaddam et al.¹⁰ showed that AHI and BP were significantly reduced by treatment with a mineralocorticoid receptor antagonist (spironolactone for 8 weeks), in 12 patients with resistant hypertension. A similar effect was also reported in 16 OSA patients with uncontrolled hypertension who received intensified diuretic therapy (metolazone + spironolactone for 7 days). This treatment reinforcement reduced AHI, BP, and overnight changes in leg fluid volume and in neck circumference.¹¹ Finally, a recent randomized controlled trial¹² that included 54 OSA patients showed that spironolactone + furosemide administered for 7 days decreased the AHI in severe male OSA patients, but less efficiently

than nutritional counseling that encouraged a sodium-restricted diet. In general, in these studies the impact of diuretics was moderate with the mean AHI reduction varying from 7 to 17 events/hour.¹⁰⁻¹²

Support for peripharyngeal edema as a cause of upper airway obstruction has been provided by acute studies linking changes in local venous intravascular volume to upper airway resistance and severity of OSA.¹⁰ In healthy volunteers induced acute increases in venous return with lower body positive pressure resulted in increases in neck circumference and upper airway resistance.¹⁹ Increases in venous pressure and fluid accumulation in the neck predisposes pharyngeal obstruction. Moreover, acute diuresis has been shown to reduce the severity of OSA in patients who were admitted with exacerbation of congestive heart failure secondary to diastolic dysfunction.⁹ These reductions in OSA occurred in association with reductions in oropharyngeal cross-sectional area (as assessed by acoustic pharyngometry), suggesting a role of peripharyngeal fluid accumulation. Intensified diuretic therapy in uncontrolled hypertensive patients with OSA has been shown to reduce the AHI and BP in proportion to the degree of attenuation of the overnight rostral fluid shift.¹¹ Fluid overload as a cause of OSA is further supported by studies showing improvements in OSA after dialysis in patients with end-stage renal disease.^{20,21} However, it has recently been demonstrated that interventions to reduce bodily fluid content in men with severe OSA promote only a limited decrease in apnea frequency, suggesting that rostral fluid displacement only partially affects OSA severity and/or that other factors prevail in determining pharyngeal collapsibility.¹² As in the present study, this underscores the differential benefits of diuretics according to OSA phenotype.

The present study has some limitations. The duration, dosage, and indication for prescribing a diuretic was not recorded at the time of AHI measurement. Our cohort includes

a large majority of OSA patients (no OSA or unknown OSA status were excluded) who might exhibit a small proportion of central sleep apnea (not reported in the electronic record). As recommended, mixed sleep apneas were included in the obstructive component. Only patients with written informed consent were included in the database. This was required for conducting the study but might constitute a potential inclusion bias, as in all cohort studies. Another limitation was the lack of data on renal disease that may have impacted the use of diuretics, especially in some subgroups of chronic heart failure patients. We also acknowledge that we did not have information for stratifying severity (left ventricular ejection fraction) allowing to differentiate heart failure with preserved versus reduced ejection fraction. However, this very large OSFP cohort (with more than 69,000 OSA patients) provided real life data on OSA patients on diuretics. The propensity score methodology used promoted robust results since it minimized selection biases and potential confounding factors.

Conclusions

These findings provide further evidence that fluid redistribution from the legs to the neck during sleep contributes to the severity of OSA in patients with hypertension and may be a significant link between these two conditions. Thus, an association between diuretic use and decreased severity of OSA in overweight or moderately obese and/or hypertensive patients has been shown. A prospective study is needed to clarify these findings and identify which class of diuretics is of interest in this distinct pathophysiological patient phenotype: overweight or moderately obese patients with OSA and hypertension.

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Author contributions

B. R., I. J.-D. and S. B. contributed to the study design, analysis and interpretation of the data, drafting and revising the manuscript. R. T., Y. G., and M. S. were responsible for acquisition of data, contributed to the discussion and reviewed the manuscript. M. J.-F. and J.-L. P. were responsible for study concept and design, supervised the study and critically revised the manuscript. J.-L. P. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7(8):687–698.
2. Lévy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primer* 2015;1:15015.
3. Lévy P, Tamsier R, Minville C, Launois S, Pépin J-L. Sleep apnoea syndrome in 2011: current concepts and future directions. *Eur Respir Rev Off J Eur Respir Soc* 2011;20(121):134–146.
4. Jullian-Desayes I, Revol B, Chareyre E, et al. Impact of concomitant medications on obstructive sleep apnoea. *Br J Clin Pharmacol* 2017;83(4):688–708.
5. Perger E, Jutant E-M, Redolfi S. Targeting volume overload and overnight rostral fluid shift: A new perspective to treat sleep apnea. *Sleep Med Rev* 2018;42:160–170.
6. Lin CM, Huang YS, Guilleminault C. Pharmacotherapy of obstructive sleep apnea. *Expert Opin Pharmacother* 2012;13(6):841–857.
7. Randerath WJ, Verbraecken J, Andreas S, et al. Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J* 2011;37(5):1000–1028.
8. Mason M, Welsh EJ, Smith I. Drug therapy for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2013;(5):CD003002.
9. Bucca CB, Brussino L, Battisti A, et al. Diuretics in obstructive sleep apnea with diastolic heart failure. *Chest* 2007;132(2):440–6.
10. Gaddam K, Pimenta E, Thomas SJ, et al. Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: a preliminary report. *J Hum Hypertens* 2010;24(8):532–537.
11. Kasai T, Bradley TD, Friedman O, Logan AG. Effect of intensified diuretic therapy on overnight rostral fluid shift and obstructive sleep apnoea in patients with uncontrolled hypertension. *J Hypertens* 2014;32(3):673–680.
12. Fiori CZ, Martinez D, Montanari CC, et al. Diuretic or sodium-restricted diet for obstructive sleep apnea—a randomized trial. *Sleep* 2018;41(4).
13. Martinez-Garcia MA, Campos-Rodriguez F, Barbé F, Gozal D, Agustí A. Precision medicine in obstructive sleep apnoea. *Lancet Respir Med* 2019;7(5):456–464.
14. Bailly S, Destors M, Grillet Y, et al. Obstructive Sleep Apnea: A Cluster Analysis at Time of Diagnosis. *PloS One* 2016;11(6):e0157318.

15. Gautier-Veyret E, Pépin J-L, Stanke-Labesque F. Which place of pharmacological approaches beyond continuous positive airway pressure to treat vascular disease related to obstructive sleep apnea? *Pharmacol Ther* 2018;186:45–59.
16. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. *Biometrics* 1996;52(1):249–264.
17. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. *Am J Epidemiol* 2006;163(12):1149–1156.
18. Austin PC. A comparison of 12 algorithms for matching on the propensity score. *Stat Med* 2014;33(6):1057–1069.
19. Shiota S, Ryan CM, Chiu K-L, et al. Alterations in upper airway cross-sectional area in response to lower body positive pressure in healthy subjects. *Thorax* 2007;62(10):868–872.
20. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med* 2001;344(2):102–107.
21. Tang SCW, Lam B, Ku PP, et al. Alleviation of sleep apnea in patients with chronic renal failure by nocturnal cycler-assisted peritoneal dialysis compared with conventional continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol JASN* 2006;17(9):2607–2616.

Tables

Table 1. Population characteristics

	Whole OSA population	OSA population without diuretics	OSA population with diuretics
N	69,564	59,781	9,783*
Age (year)	56.9 [47.4 ; 65.6]	55.9 [46.4 ; 64.6]	62.3 [54.2 ; 70.3]*
Male gender (n (%))	46272 (67)	40108 (67)	6164 (63)*
BMI (kg/m ²)	30.1 [26.5 ; 34.8]	29.9 [26.3 ; 34.5]	31.8 [28.0 ; 36.3]*
Heart failure (n (%))	1694 (2)	1123 (2)	571 (6)*
Hypertension (n (%))	27964 (40)	20639 (35)	7325 (75)*
Diabetes (n (%))	9386 (14)	7243 (12)	2143 (22)*
AHI (events/h)	28 [14 ; 43]	28 [14 ; 42]	31 [16 ; 47]*
Mean nocturnal SaO ₂ (%)	93 [92 ; 95]	93 [92 ; 95]	93 [91 ; 94]*
ESS	10 [6 ; 13]	10 [6 ; 13]	9 [5 ; 13]*

* $p < 0.01$ between OSA population with and without diuretics, for all variables.
AHI, apnea + hypopnea index; BMI, body mass index; ESS, Epworth sleepiness scale.

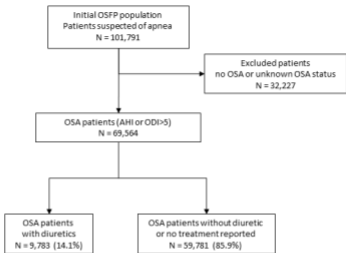
Figure legends

Figure 1. Study flow-chart

AHI, apnea-hypopnea index; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; OSFP, Observatoire Sommeil de la Fédération de Pneumologie [Sleep Registry of the French Pumonology Federation]

Figure 2. Effect of diuretics on OSA severity

BMI, body mass index; HF, heart failure; HTN, hypertension



	N Total	N Diuretics		Odds ratio [95% CI], pvalue
Overall population				
Primary analysis	42,565	8,513		0.97 [0.92; 1.02], p=0.25
Sedentariness sub-group analyses				
Sedentariness	7,082	1,438		0.96 [0.84; 1.08], p=0.48
No sedentariness	35,325	7,075		0.97 [0.91; 1.03], p=0.25
BMI sub-group analysis				
BMI ≤ 25	4,151	905		1.07 [0.91; 1.27], p=0.39
BMI]25; 30]	13,275	2,655		0.90 [0.82; 0.99], p=0.03
BMI]30; 35]	12,465	2,637		0.91 [0.82; 1.00], p=0.03
BMI >35	11,369	2,316		1.06 [0.96; 1.18], p=0.22
Heart failure sub-group analyses				
Heart failure	1,271	386		1.10 [0.82; 1.46], p=0.52
No heart failure	40,465	8,093		0.96 [0.91; 1.02], p=0.14
Sensitivity analysis HF and BMI				
HF and BMI ≤ 25	144	48		1.06 [0.45; 2.48], p=0.89
HF and BMI]25; 30]	473	146		0.95 [0.59; 1.53], p=0.84
HF and BMI]30; 35]	366	108		1.32 [0.79; 2.19], p=0.29
HF and BMI >35	288	84		1.12 [0.60; 2.10], p=0.71
HTN sub-group analyses				
Hypertension	20,777	6,214		0.84 [0.78; 0.91], p<0.01
No Hypertension	11,495	2,299		1.09 [0.99; 1.20], p=0.07
Sensitivity analysis HTN and BMI				
HTN and BMI ≤ 25	1,633	473		0.96 [0.75; 1.23], p=0.75
HTN and BMI]25; 30]	6,202	1,862		0.81 [0.71; 0.92], p<0.01
HTN and BMI]30; 35]	6,707	2,029		0.83 [0.73; 0.95], p<0.01
HTN and BMI >35	6,235	1,850		0.96 [0.84; 1.09], p=0.55

