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Original Article

ORIGINAL ARTICLE

Diuretic or sodium-restricted diet for obstructive sleep apnea—a randomized trial

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Abstract

Study Objectives: Interventions that decrease leg fluid retention reduce obstructive sleep apnea (OSA) severity in nonrandomized experiments. We aimed to investigate in a randomized trial the effect of interventions that reduce fluid volume on OSA severity.

Methods: Men diagnosed with severe OSA were randomized to receive daily spironolactone 100 mg + furosemide 20 mg or nutritional counseling to sodium-restricted diet plus placebo pill or placebo pill. All participants underwent home sleep apnea testing at baseline and after 1 week follow-up. The change in apnea–hypopnea index (AHI) was the primary outcome.

Results: The study included 54 participants and all were assessed at follow-up. The average baseline value of the AHI was similar among groups and from baseline to follow-up the AHI reduced 14.4 per cent (δ value −7.3 events per hour; 95% confidence interval, −13.8 to −0.9) in the diuretic group, 22.3 per cent (−10.7; 95% CI, −15.6 to −5.7) in the diet group, and 0.8 per cent (0.4; 95% CI, −2.5 to 3.2) in the placebo group ($p = .001$ for time × group interaction). None of the patients had their AHI returned to normal. The reduction in the total body water was 2.2 ± 2.2 L in the diuretic group ($p < .001$) and 1.0 ± 1.6 l in the low salt diet group ($p = .002$). Sleepiness and neck circumference were significantly reduced only in the diet group ($p = .007$ and $p < .001$ for the time × group interactions, respectively).

Conclusions: Interventions to reduce bodily fluid content in men with severe OSA promoted a limited decrease of apnea frequency. This finding suggests that rostral fluid displacement affects only partially the OSA severity and/or that other factors prevail in determining pharyngeal collapsibility.

Clinical Trial: Sodium-Restricted Diet and Diuretic in the Treatment of Severe Sleep Apnea (DESALT), https://clinicaltrials.gov/ct2/show/NCT01945801, ClinicalTrials.gov number: NCT01945801.

Statement of Significance

Fluid retention as a part of the pathogenesis of obstructive sleep apnea (OSA) has been proposed and demonstrated in nonrandomized experiments. This is the first randomized controlled parallel study demonstrating reductions in the apnea–hypopnea index of about 10%–20% using diuretics and low-salt diet. Although our data extend the literature and confirm the participation of fluid retention in determining OSA severity, the other mechanisms involved are apparently more important in OSA pathogenesis. The actual magnitude of the association between fluid retention and OSA severity remains to be confirmed. Further research is necessary to confirm the response to interventions that reduce fluid retention in long-term interventions and in different OSA populations.

Key words: sodium-restricted diet; diuretics; fluid shifts; obstructive sleep apnea

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Introduction

Overnight displacement of fluid from the lower to the upper body has been proposed as a pathogenic mechanism of obstructive sleep apnea (OSA) [1, 2]. Supporting this concept, previous studies demonstrate that recumbence-dependent rostral shift of fluid increases neck fluid volume and circumference [3–5] and OSA severity [6]. Using compression trousers to force extracellular fluid out from the legs increases pharyngeal resistance [7, 8] and upper airway collapsibility [9], while reducing pharyngeal cross-sectional area.

The use of compression stockings seems to reduce the apnea–hypopnea index (AHI) in people with [10] and without peripheral venous insufficiency [11]. OSA severity and snoring have also been decreased by other methods of avoiding leg fluid accumulation, such as calf contraction while sitting [12] and diuretic therapy [13–15]. Moreover, in participants older than 40 years, acute saline infusion during stage 2 sleep substantially increases the AHI and neck circumference [16].

Despite the available evidence, no randomized trial has yet demonstrated that reducing the bodily fluid content changes the AHI. The present study was designed to test the hypothesis that fluid-reducing strategies, such as diuretic use or a sodium-restricted diet, can decrease OSA severity. For this purpose, we conducted a randomized clinical trial in which men with severe OSA underwent 1 week of intervention and had their AHI reassessed subsequently.

Methods

Study design and supervision

This was a three-arm, parallel, placebo-controlled, explanatory randomized clinical trial. Men with severe OSA received drug, diet, or placebo pill. The institutional Ethics Committee approved the study under the number 13-0272. This committee is accredited by the Office of Human Research Protection as an Institutional Review Board (IRB0000921). The protocol was registered at clinicaltrials.gov under the number NCT01945801 and has been published previously [17].

Participants and protocol

Candidates were drawn from a database of full-night in-laboratory polysomnographies performed as previously described [18] at a university-affiliated sleep laboratory. Immediately after undergoing polysomnography and having severe OSA confirmed, the patients were approached by telephone. The inclusion criteria were as follows: men aged 18–60 years with AHI greater than 30 events per hour, predominantly obstructive, and body mass index (BMI) below 35 kg/m^2. Exclusion criteria were as follows: receiving treatment for OSA; use of diuretics or substances with action in the central or peripheral nervous system; peripheral venous or lymphatic insufficiency; any cardiac, renal, or neurological disease; or physical, mental, or social condition impairing the ability to participate in the trial.

Those willing to volunteer were invited to attend visit 1, in fasting, at the hospital Clinical Research Center for providing written informed consent, and being randomized. The urine container and the respiratory polygraphy monitor were handed to the patient and were returned in the next day, during visit 2. The patients randomized to diet started dieting only after visit 2. The respiratory polygraphy recorder and the urine container were returned and processed the next morning during visit 2. One week later, the patients returned in fasting for visit 3. Blood sampling, bioelectrical impedance, and anthropometric measurements were repeated. The urine container and the sleep monitor were again handed to the patient and were returned in the next day, during visit 4.

Home sleep apnea testing

Patients underwent home sleep apnea testing before and after the interventions, using the Somnocheck Effort (Weinmann GmbH, Hamburg, Germany), a monitor with a SCOPER categorization of S_0,C_4,O_{1x},P_2,E_4,R_2 (Sleep, Cardiovascular, Oximetry, Position, Effort, Respiratory) [19], that was validated against polysomnography by our group [20]. A nasal cannula recorded airflow and snoring; a pulse oximeter recorded oxygen saturation and heart rate. Body position and respiratory effort were also recorded by the same monitor.

Respiratory events lasting 10 s or longer were scored manually by one certified technician. OSA was defined by a 90 per cent or greater drop in flow; hypopnea by a 30 per cent or greater drop in flow accompanied by either a 3 per cent or greater oxygen desaturation or an autonomic arousal identified by an increase of at least six beats per minute in heart rate. The AHI was calculated dividing the total of apneas and hypopneas by the number of hours of artifact-free recording. All records were reviewed by a certified sleep medicine specialist.

Interventions

The participants were randomized to three arms: placebo pill, combination of placebo pill and sodium-restricted diet, or spironolactone 100 mg plus furosemide 20 mg (Lasilactone). Volunteers took the pills once daily in the morning during 7 days.

The sodium-restricted diet group received a regimen aiming a maximum intake of 3 g of sodium per day (equivalent to 7.5 g of sodium chloride). The participants received a handout describing the diet (available as Supplementary Material). During the week, a phone call by the nutritionist helped us to ensure the adherence to the program. To facilitate adherence, the dietary intervention was initiated only after confirming that the volunteer would not participate in social events or travels during this week. They also could photograph dishes and send to the nutritionist for on the spot consultation, before eating or buying a food item. Dietary composition was aligned with standard recommendations [21]. In brief, sodium restriction was obtained by enforcing the following rules: (1) do not use salt in cooking; (2) do not use the salt shaker; (3) to flavor foods, use spices, herbs, and other seasonings, such as olive oil, lemon, herbs, garlic, onion, parsley, and chives, instead of salt; (4) do not eat any industrialized food, such as sauces, soups, sausages, canned food, frozen, salted snacks, cheese, salami, or sausages; (5) eat fresh salads and vegetables; (6) do not add high-sodium seasonings, such as soy sauce; and (7) eat fruit for dessert; do not eat baked desserts. The volunteers in the placebo and diuretic arms were instructed to maintain their eating habits during the study week.

Outcomes assessment

Outcomes were assessed at baseline and at 1 week of intervention. The primary outcome was the change in OSA severity assessed by the group × time interaction of AHI. This value was obtained pre- and post-intervention by home sleep apnea testing. Lowest oxygen saturation and excessive daytime sleepiness, assessed by the Epworth sleepiness scale [22], were secondary outcomes. To confirm the physiological impact of the interventions, we also analyzed at baseline and at 1 week of intervention the following variables: anthropometrics, total and extracellular water, renal parameters, electrolytes, and blood pressure.

The assessment of body composition was performed using a tetrapolar bioelectrical impedance device (Biodynamics, model 450, WA, USA) [23, 24]. We performed all measurements in the morning, while fasting, after at least 4 hor without ingesting any liquid, during the same visit scheduled for blood sampling. Body weight was measured within 100 g intervals and height within 0.1 cm using a scale with a stadiometer, with the participants wearing scrubs. Circumferences were measured with a graduated measuring tape. Neck circumference was assessed above the thyroid cartilage; waist, at the narrowest point between the lowest rib and the iliac crest; ankle, 1 cm above the medial malleolus.

Blood samples were collected in the early morning (7–9 am) after fasting for at least 12 hr. Biochemical analyses and assays employed are described in Supplementary Table S1. The blood pressure reported was the average of two valid blood pressure measurements taken in the seated position, employing the HEM 7130 device (OMRON Healthcare, Inc., Kyoto, Japan).

The adverse events were investigated at the follow-up interview by open questions. Specific questions were made regarding symptoms potentially related to the diuretics, as dizziness, cramps, dehydration, and hypotension.

An independent researcher who was not involved in the study generated the randomization table at randomization.com. The allocation sequence was created in nine blocks of six. The placebo pills were manufactured in capsules indistinguishable from those of the industrialized brand-name diuretic. The three groups received the capsules stored in identical flasks, coded for each participant according to the randomization table. The researchers involved in the assessment of the outcomes were blind to the group assignment. The nutritionist who delivered the nonblinded diet intervention was unaware of the pills supplied to the remaining groups and was not involved in other steps of the protocol. The home sleep apnea testing tracings were e-mailed to a third-party certified scorer unaware of the existence of the study. Patients' blinding was assessed by the Bang's blinding index [25]. At the end of the trial, the participants answered the question of whether they received an active drug, a placebo, or did not identify which type of pill they were taking. Data collectors and health care providers were not tested for blinding. Patients' compliance with the low-salt diet was verified by dosage of 24 hr urinary sodium before and after the intervention; compliance with diuretics was assessed by pill count.

Statistical analysis

Sample size calculation was performed for tests of means difference after repeated measures, within-between interactions, analysis of variance approach, using the G*Power software [26]. For an expected effect size of 0.25, a power of 90 per cent, an α error probability of 5 per cent, and a correlation between two repeated measures of 0.5, in a three-arm design, the required sample size was calculated as 18 in each group, totaling 54 individuals.

Data are presented as means and standard deviation in tables and as mean and one standard error of mean in the figure. Most statistical analyses were performed using SPSS software (v. 18, SPSS, Inc., Chicago, IL, USA). The baseline comparisons among groups were performed using one-way ANOVA. Tests for significance of differences between and within groups, from baseline to follow-up, and time × group interactions were performed using generalized estimating equations (GEE). For all analyses, outcome variables were tested by time (before and after intervention) and group (diet, diuretic, and placebo) interaction. Pairwise comparisons for diet vs. placebo, diuretic vs. placebo, and diet vs. diuretic were performed with the number of comparisons in each analysis automatically adjusted by the Bonferroni's post hoc tests algorithm of SPSS. The total body water content in liters and the body mass index in kg/m^2 were included individually and together in the GEE model to test the significance of their participation in the time × group interaction. Cohen's d statistic available at www.uccs.edu/~lbecker/ was used to calculate the effect size of the differences between active treatments and placebo conditions using the following formula: $d = M_1 - M_2/s_{pooled}$, where $s_{pooled} = \sqrt{[(s_1^2 + s_2^2)/2]}$ [27]. M denotes the mean and s, standard deviation. The Bang's blinding index was calculated using Stata software (v. 11, Stata Corp LP., College Station, TX, USA). Results with a probability of α error lower than 0.05 were considered statistically significant.

Results

Figure 1 depicts the participant enrollment and randomization processes, performed from December 2013 to August 2015. Despite the effort to proceed with the enrollment before the participants had a prescription for OSA, one quarter of the excluded candidates had already started CPAP use. Two volunteers withdrew from the study; one day after randomization, one due to an unexpected travel assignment, and one due to unwillingness to comply with his allocation to the sodium-restricted diet. Each volunteer was replaced by the next enrolled participant. A total of 54 participants successfully completed the baseline and follow-up home sleep apnea testing and visits. Analyses, therefore, were by modified intention-to-treat.

Participants had in-laboratory screening polysomnography diagnostic of severe OSA and the typical OSA characteristics, i.e. high BMI, low level inflammatory activity, fasting glucose, and serum cholesterol in the upper limit. These and other characteristics were similarly distributed among the three experimental groups (Table 1).

Figure 2 displays the individual values and mean estimates of AHI in the three groups at baseline and follow-up. Time differences were significant for both intervention groups. The time × group interaction was significant. The δ AHI in the diuretics group is nonsignificantly different from the δ AHI in the placebo group. The full results of the GEE model with Bonferroni's correction are shown in Supplementary Table S2. When compared with the placebo group, the effect size of the δ AHI, measured

by Cohen's *d*, was –1.26 in the diet group and –0.71 in the diuretic group.

The secondary outcomes and variables of physiological interest are presented in Tables 2 and 3. Diet vs. diuretic group contrasts were nonsignificant for all variables. The time × group interaction was significant for Epworth sleepiness scale, neck circumference, bodily total water content, extracellular water, body weight, BMI, systolic and diastolic blood pressure, aldosterone concentration, plasma renin activity, and 24 hr urinary sodium.

No significant difference was observed in the baseline blood pressure measurements. Inclusion of blood pressure in the GEE model did not produce any significant change in the AHI time × group interaction.

The correlations between δ total body water content and change in OSA severity markers (δ AHI and δ lowest SaO_2) were nonsignificant and small (Table 4). The ρ values were small in diet and diuretic groups (–0.1 and 0.05, respectively). Combining both intervention groups, the ρ value remains negligible (0.07). Nonsignificant results are seen also for OSA severity markers correlated with δ urinary sodium and δ BMI (Table 4).

To verify the effect of total body water and BMI on the time × group interaction for change in AHI, further analyses in GEE models were attempted (Table 5). The interaction remained highly significant after the introduction of these two possible mediators in the model.

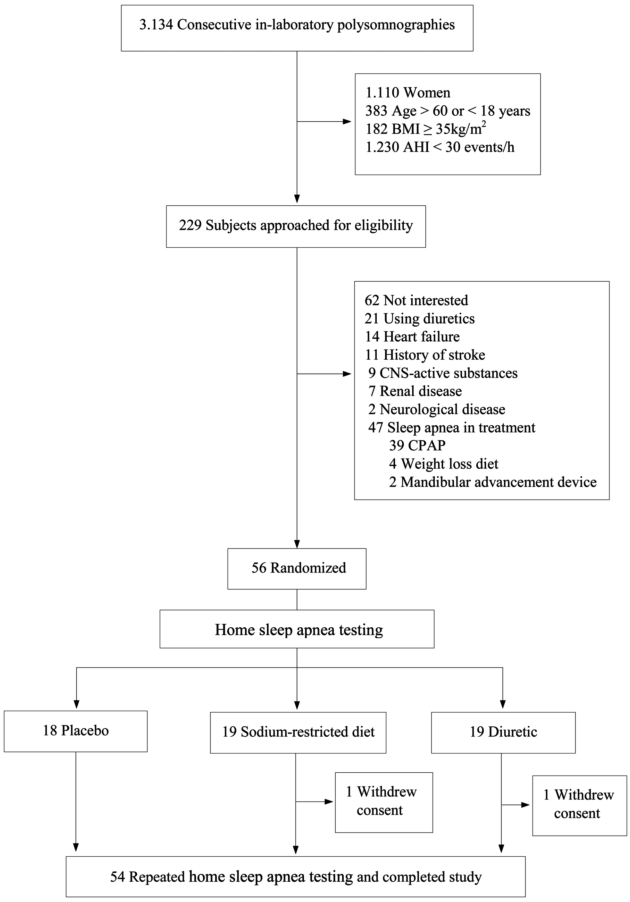

Figure 1. Flow diagram of the patients included in study. AHI = apnea–hypopnea index; BMI = body mass index; CNS = central nervous system; CPAP = continuous positive airway pressure.

The blinding questionnaire was completed by 51 participants. Among the participants receiving the placebo pill (the placebo and diet groups), 79 per cent answered "don't know," 12 per cent guessed the opposite treatment (active drug), and 9 per cent guessed correctly. In the diuretic group, 67 per cent answered "don't know," 22 per cent guessed the opposite treatment (placebo pill), and 11 per cent guessed correctly. The Bang's blinding index was 0.03 (95% CI, –0.10 to 0.16; $p = .35$) in the placebo pill groups, and 0.11 (95% CI, –0.11 to 0.33; $p = .20$) in the diuretic group. These results indicate that participants were unaware of the assigned pill treatment.

Adverse events were infrequent and not serious. One patient in the placebo group complained of headache. Polyuria was reported by one patient in the diet group, and four in the diuretic group. Additionally, among the participants treated with diuretic, three complained of nocturia and one of malaise.

Discussion

Our findings show that two interventions aiming to reduce bodily salt and water content diminished the AHI among male patients diagnosed with severe OSA. These results from an explanatory randomized clinical trial are in agreement with previous findings of nonrandomized observational studies. The placebo arm of our study showed only minimal changes in the AHI, supporting the reproducibility of the home sleep apnea testing. The reduction of AHI occurring in the diet and diuretic groups suggests a volume-related mechanism of action, common to both interventions, reducing the possibility of putative specific or pleiotropic effects of furosemide and/or spironolactone on neural or humoral mechanisms of OSA.

This trial tested the hypothesis that fluid-reducing strategies can decrease OSA severity. However, no significant correlations were found among the variables in Table 4. The small correlation coefficients indicate that only a minor fraction of the change in OSA severity is explained by change in total body water content. The magnitude of change in AHI was similar with both fluid-reducing interventions. Regarding the relative percent effect of both approaches on AHI (14 and 22 per cent), it was relatively small.

One obvious reason for the lack of AHI-to-water content correlation is an inadequate accuracy of the bioimpedance instrumentation. Also, no patient was dehydrated. Since water in the diet group and water and salt in the diuretic group were ingested ad libitum, the level of fluid depletion obtained in the present study may have been insufficient to prevent the rostral fluid shift; the rostral fluid displacement could have been reduced but not eliminated by the degree of bodily fluid reduction obtained. It is possible that even intensive diuresis is unable to suppress rostral fluid displacement. Studies that confirmed a postural effect on fluid distribution [28, 29] have not tested the effect of diuretics or salt restriction. Additionally, the other pathophysiological determinants of sleep-related airway obstruction, such as fat tissue accumulation [30] and recumbence-dependent displacement [31], craniofacial features, and airway control abnormalities [32–34], may prevail over fluid displacement in determining OSA severity. More precise documentation of segmental fluid content and of its displacement will be necessary to unravel the meanders of fluid–apnea relationship.

Table 1. Characteristics of the patients at baseline by study group

Characteristics	Placebo, *n* = 18	Sodium-restricted diet, *n* = 18	Diuretic, *n* = 18
Age—yr	46.5 ± 7.4	45.2 ± 8.3	42.9 ± 10.6
Waist circumference—cm	101.0 ± 6.7	100.6 ± 7.3	100.0 ± 8.4
Use of antihypertensive medication—*n*	3	2	1
Biochemical analysis			
Ultrasensitive C-reactive protein—mg/dL	2.8 ± 3.2	2.0 ± 1.6	3.3 ± 3.5
Cholesterol—mg/dL			
Total	206.7 ± 37.9	204.3 ± 22.2	194.6 ± 32.8
High density lipoprotein	41.5 ± 6.8	39.1 ± 6.4	37.8 ± 5.4
Low density lipoprotein	131.2 ± 34.9	135.7 ± 22.4	126.9 ± 22.8
Triglycerides—mg/dL	170.0 ± 91.6	147.4 ± 55.0	149.6 ± 58.8
Fasting glucose—mg/dL	105.8 ± 34.6	94.9 ± 8.5	105.4 ± 23.9
Pre-enrollment in-laboratory polysomnography			
Apnea-hypopnea index—events/hr	44.3 ± 11.5	49.3 ± 19.0	47.6 ± 19.5
Respiratory disturbance index—events/hr	46.2 ± 11.5	51.1 ± 18.6	49.7 ± 19.1
Total sleep time—min	390 ± 47	417 ± 48	383 ± 44
Rapid eye movement stage—%	14.4 ± 4.9	13.4 ± 5.7	13.4 ± 4.8
Non-rapid eye movement stage 1—%	6.9 ± 2.7	6.1 ± 2.7	6.1 ± 2.9
Non-rapid eye movement stage 2—%	58.9 ± 12.0	61.5 ± 13.7	62.3 ± 9.8
Non-rapid eye movement stage 3—%	11.4 ± 8.5	11.2 ± 9.1	11.1 ± 8.6
Sleep efficiency—%	86.5 ± 9.6	87.4 ± 7.6	86.7 ± 8.5
Mean oxygen saturation—%	92.9 ± 1.5	93.2 ± 1.3	92.7 ± 3.4
Lowest oxygen saturation—%	77.0 ± 5.3	77.4 ± 7.3	75.7 ± 10.9

Apnea–hypopnea index: total apnea + hypopnea events divided by the number of hours of sleep; Respiratory disturbance index: total apnea + hypopnea + respiratory effort-related arousals events divided by the number of hours of sleep; Sleep efficiency: total sleep time divided by total recording time, in percentage. Values are mean ± standard deviation.

The results obtained regarding the variables of interest were mostly those predicted by the intervention type. Both diuretic and diet groups showed similar total body water reduction from baseline to follow-up. It is important to notice that 24 hr urinary sodium was reduced only in the low-salt diet group, confirming true dietary sodium restriction. The 24 hr urinary sodium excretion reduced 35mEq/L (2.0 g of salt) in the diuretic group and 117mEq/L (6.7 g of salt) in the diet group. In the placebo group, sodium excretion increased 18mEq/L (1.0 g of salt).

Although many possible diuretics could have been employed, the choice of spironolactone/furosemide combination was considered adequate for several reasons: (1) the dose of 20 mg is recommended for the management of patients with hypertension, without heart or chronic kidney disease; (2) all previous work on OSA–diuretics relationship [12–14] included spironolactone, in consideration of reports that patients with OSA have at least some degree of hyperaldosteronism [35]; and (3) spironolactone would promote a potassium-sparing effect and antagonize occasional adverse effects of furosemide.

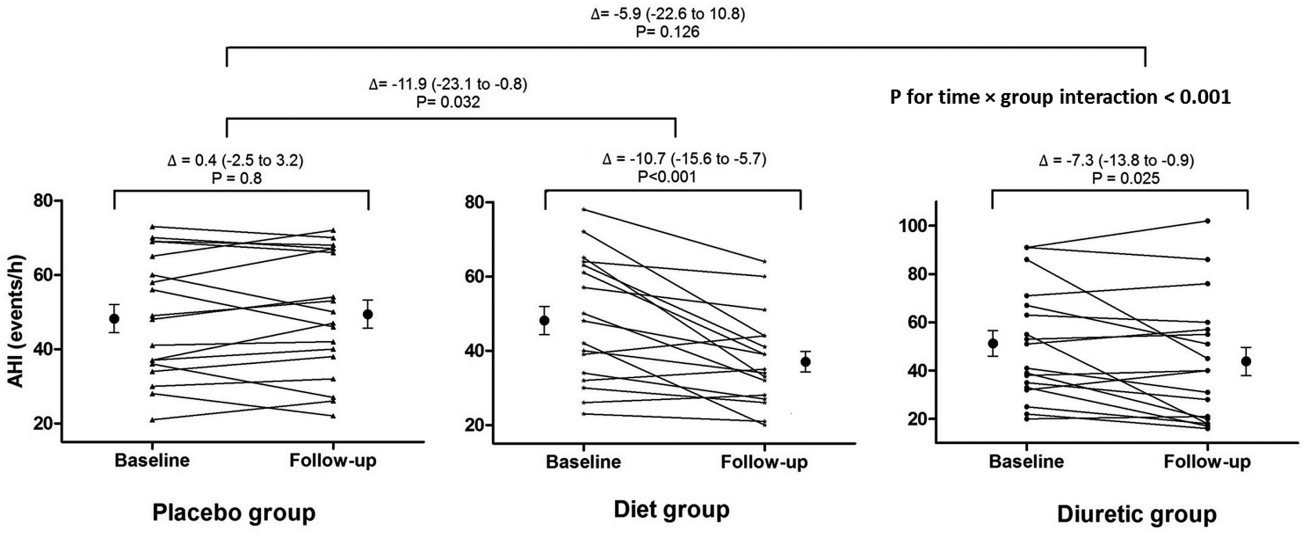

Figure 2. Plot of the changes in AHI in the three intervention groups at baseline and follow-up. The error bars represent one standard error of the mean. The within-participant and between-group significances were obtained by generalized estimating equations. Bonferroni's correction was applied for between group comparisons. Values in parenthesis represent 95% confidence interval. No significant AHI change was seen within the placebo group. Both diet and diuretic groups showed significant AHI reduction at follow-up. The differences between placebo and diuretic and between diet and diuretic groups were nonsignificant after adjustment.

Table 2. Secondary outcome measures in the study participants

Outcome	Baseline value	Mean δ follow-up minus baseline (95% CI)	Bonferroni *p* value for δ treatment versus placebo	*P* value for time × group interaction	Effect size treatment vs. placebo
Out-of-center polygraphy					
Lowest oxygen saturation—%					
Placebo	77.5 ± 7.1	0.8 (–4.2 to 2.5)	—	.6	—
Diet	77.9 ± 7.8	1.5 (–0.9 to 3.9)	.7		.11
Diuretic	76 ± 11.3	–0.1 (–2.6 to 2.4)	.4		.14
Epworth Sleepiness Scale					
Placebo	10.7 ± 5.4	–0.6 (–1.2 to 0.1)	—	**.007**	—
Diet	11.6 ± 4.8	–2.3 (–3.2 to –1.3)	**.02**		.98
Diuretic	13.2 ± 5.3	–0.5 (–1.4 to 0.4)	.9		.06
Circumferences—cm					
Neck					
Placebo	42.9 ± 2.2	–0.1 (–0.6 to 0.3)	—	**<.001**	—
Diet	43.3 ± 2.5	–1.2 (–1.6 to –0.8)	**.01**		1.26
Diuretic	42.3 ± 2.9	0.1 (–0.5 to 0.7)	.8		.17
Ankle					
Placebo	24.3 ± 1.3	–0.2 (–0.6 to 0.1)	—	.7	—
Diet	24.9 ± 2.1	–0.4 (–0.8 to 0.1)	.9		.22
Diuretic	23.7 ± 2.6	0.1 (–0.8 to 0.7)	.7		.23
Urinary sodium—mEq/24 hr					
Placebo	187 ± 63	–18.3 (–51.5 to 14.9)	—	**.006**	—
Diet	226 ± 98	–117 (–169 to –65.2)	**.009**		1.43
Diuretic	199 ± 67	–35.3 (–77.0 to 6.3)	.9		.65
Total body water—L					
Placebo	48.6 ± 5.2	0.4 (–1.2 to 4.1)	—	**<.001**	—
Diet	50.3 ± 5.3	–1.1 (–1.7 to –0.4)	**.008**		.80
Diuretic	49.9 ± 7.5	–2.2 (–3.2 to –1.2)	**<.001**		1.27
Extracellular water—L					
Placebo	19.9 ± 2.2	0.1 (–0.3 to 0.4)	—	**<.001**	—
Diet	20.3 ± 2.5	–0.6 (–1.0 to 0.2)	**.02**		1.03
Diuretic	20.2 ± 3.3	–1.7 (–2.2 to –1.2)	**<.001**		2.07

Data are shown as mean ± standard deviation and as follow-up minus baseline change (95% confidence interval).
P values were obtained from generalized estimating equations with Bonferroni's correction for multiple comparisons.
Significant results are shown in bold typeface.

Taken together, our findings validate the hypothesis that excess fluid influences OSA severity [36]. We observed further significant and pathophysiologically meaningful changes in several potential mediators and consequences of these interventions. However, the present study was neither designed nor powered to address outcomes other than the effect on AHI.

Previous nonrandomized reports have tested the effect of diuretics on OSA severity. Bucca et al. [13], in 2007, employed IV furosemide 20mg, and spironolactone 100mg, bid for 3 days, in patients with diastolic heart failure and observed a reduction of the AHI from 75 to 57 events per hour (24 per cent). In 2010, Gaddam et al. [14] added spironolactone to the antihypertensive therapy of patients with resistant hypertension, obtaining a decline of the AHI from 40 to 22 events per hour (45 per cent). In 2014, Kasai et al. [12] intensified the diuretic therapy of patients with uncontrolled hypertension by adding metazolone 2.5 mg plus spironolactone 25 mg daily for 7 days, obtaining a decrease in AHI from 58 to 49 events per hour (15 per cent). In the present study, the AHI was reduced by 14 per cent with diuretics, and by 22 per cent with diet, 18 per cent in average. This is in close agreement with the study of Kasai et al. [12], suggesting that the participation of fluid retention in determining OSA severity is around 10%–20% in nonedematous patients. In cases with more prominent fluid retention as those of diastolic heart failure, diuretics reduce the AHI by 24 per cent [13] and in patients with resistant hypertension, spironolactone reduced the AHI by 45 per cent [14], much larger than observed in our sample in terms of percent change but virtually identical to what we observed with diet in terms of effect size (1.27 vs. 1.26 standard deviations). Smaller responses to interventions in our study were expected, since usually effect sizes tend to decrease as the evidence level increases [37].

In heart failure, a daily intake of more than 2.4 g of sodium (6 g of sodium chloride) predicts moderate-to-severe sleep apnea [38], but no study has tested the effect of a sodium-restricted diet in the usual patient with OSA. The present investigation is the first interventional study to address whether sodium restriction interferes in OSA severity. The differences in changes of AHI, total body water, and extracellular water between the groups are nonsignificant. The fact that diet and diuretics reduce the AHI with different magnitudes may be due only to chance as the 95% confidence intervals of the δ AHI in these two groups overlap (Figure 2). The same reasoning applies to the differences of δ total body water in diet and diuretic groups that are within the confidence limits. Furthermore, changes in response of sleepiness and neck circumference are also within the 95% confidence limits of the mean of the two intervention groups: diuretic and diet (Table 2). Although both treatments aimed to reduce bodily fluid content, occasional differential effects

Table 3. Variables of physiological interest in the study participants

Outcome	Baseline value	Mean δ follow-up minus baseline (95% CI)	Bonferroni *P* value for δ treatment versus placebo	*P* value for time × group interaction
Body weight, kg				
Placebo	89.4 ± 2.3	0.06 (–0.3 to 0.2)	—	
Diet	93.0 ± 2.6	–1.3 (–1.9 to –0.8)	**<.001**	**<.001**
Diuretic	91.3 ± 3.0	–0.9 (–1.3 to –0.6)	**<.001**	
BMI, kg/m^2				
Placebo	29.3 ± 0.6	–0.06 (–0.17 to 0.04)	—	
Diet	30.5 ± 0.8	–0.4 (–0.6 to –0.2)	**<.001**	**.004**
Diuretic	29.8 ± 0.7	–0.3 (–0.4 to –0.1)	**<.001**	
Office blood pressure, mm Hg				
Systolic				
Placebo	121.6 ± 1.5	2.3 (–3.3 to 8.0)	—	
Diet	127.0 ± 2.5	–7.4 (–11.2 to –3.5)	**<.001**	**.016**
Diuretic	124.1 ± 1.9	–2.4 (–5.8 to 1.0)	.2	
Diastolic				
Placebo	84 ± 1.6	1.4 (–1.8 to 4.6)	—	
Diet	85 ± 2.4	–4.8 (–7.8 to –1.7)	**.002**	**.02**
Diuretic	85 ± 1.8	–2.8 (–6.0 to 0.5)	.09	
Serum biochemical analyses				
Aldosterone—ng/dL				
Placebo	11.7 ± 2.1	–0.08 (–2.7 to 2.6)	—	
Diet	9.1 ± 1.1	15.1 (6.6 to 23.5)	**<.001**	**<.001**
Diuretic	9.6 ± 1.7	49.2 (31.9 to 66.4)	**<.001**	
Renin—ng/mL/hr				
Placebo	4.4 ± 1.9	–1.4 (–3.2 to 0.4)	—	
Diet	3.7 ± 1.3	2.6 (–2.5 to 7.7)	.3	**<.001**
Diuretic	1.7 ± 0.3	7.6 (4.2 to 11.1)	**<.001**	
Creatinine—mg/dL				
Placebo	0.9 ± 0.08	0.05 (–0.1 to 0.2)	—	
Diet	1.0 ± 0.04	0.1 (–0.01 to 0.2)	.07	.65
Diuretic	1.0 ± 0.05	0.2 (–0.1 to 0.5)	.2	
Urea–mg/dL				
Placebo	29.2 ± 2.3	4.0 (0.2 to 7.9)	—	
Diet	36.2 ± 2.6	3.9 (–1.5 to 9.3)	.16	.76
Diuretic	32.8 ± 2.7	7.2 (–0.6 to 14.9)	0.07	
Sodium–mEq/L				
Placebo	135.6 ± 5.0	8.0 (0.1 to 15.8)	—	
Diet	142.3 ± `2.8	–3.0 (–8.6 to 2.6)	.3	.08
Diuretic	140.8 ± 1.8	–0.3 (–3.1 to 2.5)	.8	
Potassium—mEq/L				
Placebo	4.2 ± 0.1	0.4 (–0.1 to 0.8)	—	
Diet	4.5 ± 0.1	0.2 (0.003 to 0.4)	**.05**	.79
Diuretic	4.5 ± 0.1	0.3 (–0.2 to 0.8)	.2	
Urinary biochemical analyses				
Creatinine—mg/24 hr				
Placebo	1709.8 ± 78.9	–211 (–410 to –11.7)	—	
Diet	1964.7 ± 82.2	–175 (–441 to 90.6)	.2	.5
Diuretic	1721.0 ± 81.7	–75.8 (–229 to 77.5)	.3	
Potassium—mEq/24 hr				
Placebo	66.2 ± 4.8	–9.1 (–20.3 to 2.03)	—	
Diet	81.8 ± 7.6	–8.3 (–21.5 to 4.8)	.2	.35
Diuretic	54.6 ± 3.8	–0.8 (–7.5 to 5.9)	.8	
Urea—g/24 hr				
Placebo	27.2 ± 1.6	–2.6 (–6.1 to 0.9)	—	
Diet	30.3 ± 1.8	0.6 (–5.0 to 6.2)	.8	.29
Diuretic	26.3 ± 1.7	1.1 (–2.2 to 4.4)	.5	

Data are shown as mean ± standard deviation and as follow-up minus baseline change (95% confidence interval).
P values were obtained from generalized estimating equations with Bonferroni's correction for multiple comparisons.
Significant results are shown in bold typeface.

Table 4. Correlations between two OSA severity outcomes (δ AHI and δ lowest SaO_2) and three treatment outcomes in placebo and intervention groups

Interventions	Outcomes	δ AHI (events/hour)	δ lowest SaO_2 (%)
Placebo (*n* = 18)	Delta total body water (L)	−0.193 (*p* = .457)	−0.025 (*p* = .925)
	Delta urinary sodium (mEq/L)	0.113 (*p* = .654)	−0.456 (*p* = .057)
	Delta body mass index (kg/m²)	0.411 (*p* = .102)	−0.207 (*p* = .424)
Diet (*n* = 18)	Delta total body water (L)	−0.100 (*p* = .694)	−0.170 (*p* = .501)
	Delta urinary sodium (mEq/L)	−0.132 (*p* = .602)	0.085 (*p* = .737)
	Delta body mass index (kg/m²)	0.182 (*p* = .469)	−0.101 (*p* = .690)
Diuretics (*n* = 18)	Delta total body water (L)	0.051 (*p* = .840)	0.270 (*p* = .279)
	Delta urinary sodium (mEq/L)	0.122 (*p* = .630)	−0.380 (*p* = .120)
	Delta body mass index (kg/m²)	−0.208 (*p* = .408)	−0.066 (*p* = .793)
Diet or Diuretics (*n* = 36)	Delta total body water (L)	0.071 (*p* = .682)	0.163 (*p* = .341)
	Delta urinary sodium (mEq/L)	−0.087 (*p* = .615)	−0.183 (*p* = .286)
	Delta body mass index (kg/m²)	−0.061 (*p* = .724)	−0.089 (*p* = .605)

Values are Spearman's rho (significance) of the correlations.
AHI = apnea–hypopnea index; SaO_2 = oxygen saturation in arterial blood.

by these two interventions could be also explained by differences in vascular permeability, hydroelectrolytic balance, and osmotic aspects of fluid displacement. These alternative mechanisms were not approached in the present work.

Since our interventions with salt restriction and diuretics are also treatments for heart failure, it is possible that our severe patients with OSA with more fluid apt to be displaced from the legs to the neck are also the ones more likely to have subclinical right ventricle dysfunction. Echocardiographic determination of right ventricle function should be performed in future research.

Table 5. Tests of model effects of dependent variable apnea–hypopnea index by time and group. Models 2 to 4 include adjustment for total body water, body mass index, and both

	Type III		
Source	Wald chi-square	*df*	*P*
Model 1: (Intercept), time, group, time × group			
(Intercept)	372.642	1	**<.001**
Time	16.305	1	**<.001**
Group	1.885	2	.390
Time × Group	16.359	2	**<.001**
Model 2: (Intercept), time, group, time × group, total body water			
(Intercept)	1.247	1	.264
Time	12.309	1	**<.001**
Group	1.995	2	.369
Time × Group	9.739	2	**.008**
Total body water (L)	1.909	1	.167
Model 3: (Intercept), time, group, time × group, body mass index			
(Intercept)	0.112	1	.738
Time	13.367	1	**<.001**
Group	2.737	2	.255
Time × Group	14.253	2	**.001**
Body mass index (kg/m²)	2.701	1	.100
Model 4: (Intercept), time, group, time × group, body mass index, total body water			
(Intercept)	0.008	1	.929
Time	11.931	1	**.001**
Group	2.581	2	.275
Time × Group	10.072	2	**.006**
Body mass index (kg/m²)	1.563	1	.211
Total body water (L)	0.614	1	.433

Significant results are shown in bold typeface.

In renal patients, a recumbence-dependent venous pressure increase leads to internal jugular distension as shown by Elias et al. [39]. Jugular distension explains 64 per cent of the AHI variance in that study but was not determined in our analysis.

The randomized design warrants the internal validity of our study, but its external validity is limited as the sample includes only patients with severe OSA and only male patients. The sample was composed exclusively of men based, in part, on the report by Su et al. [40], which described no change in the pharyngeal collapsibility of women acutely subjected to positive pressure on the legs. Those authors considered that anatomical differences might prevent the occurrence of rostral fluid shift in women, making females unsuitable participants in the investigation of these mechanisms. Furthermore, the menstrual cycle influences fluid retention and apnea severity and would be a difficult to control for factor [41].

Another limitation may be an insufficient dose of furosemide preventing the full fluid-reducing effect of a diuretic intervention. Future research could evaluate the effect of greater doses and of using longer-acting loop diuretics to achieve maximal fluid depletion.

The sodium restriction also could be considered insufficient to produce the maximal fluid depletion since the water volume measured by bioimpedance did not reduce as much with diet as with diuretic. This might be not the case since, besides the reduction in salt ingestion being highly significant, no concerns can be raised in terms of adherence to the diet. The 24 hr urinary sodium excretion in the seventh day was 109 mEq, indicating an ingestion of approximately 6.3 g of sodium chloride daily, below the 7 g ingestion aimed in the present study. More strict nutritional recommendations would be difficult to implement in practical terms.

It was beyond the scope of the present study to test the therapeutic effectiveness or clinical relevance of long-term diuretic and diet interventions for OSA. The 1 week duration was selected as an intervention time that was long enough to promote fluid loss. It is uncertain whether the presently observed effects will improve or regress if the protocol is maintained for longer periods after which the full activation of hydroelectrolytic homeostatic mechanisms takes place. Future studies should investigate the long-term application of approaches with lower diuretic doses or of diets less restricted in sodium. Clinical trials with large samples and long-term follow-up will be necessary to clarify the role and viability of altering fluid retention for OSA therapy.

In conclusion, the present randomized clinical trial indicates that interventions to reduce bodily fluid content in men with severe OSA promote a limited decrease of apnea frequency. Our findings suggest that such interventions affect only partially the rostral fluid displacement and/or rostral fluid displacement affects only partially the OSA severity and/or other pathophysiological factors prevail in determining airway obstruction.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Notes

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