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Impact of kidney transplantation on sleep apnea severity: A prospective polysomnographic study

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Fluid overload has been associated with a high prevalence of sleep apnea (SA) in patients with end-stage kidney disease (ESKD). In this prospective study, we hypothesized that improvement in kidney function and hydration status after kidney transplantation (Tx) may result in an improvement in SA severity. A total of 196 patients on the kidney Tx waiting list were screened for SA using home nocturnal polysomnography (PSG) to measure the apnea-hypopnea index (AHI) and underwent bioimpedance to assess body composition. Of 88 participants (44.9%) with SA (AHI ≥ 15/h), 42 were reassessed 6 months post-Tx and were compared with 27 control patients. There was a significant, but small, post-Tx improvement in AHI (from 44.2 ± 24.3 to 34.7 ± 20.9/h, P = .02) that significantly correlated with a reduction in fluid overload (from 1.8 ± 2.0 to 1.2 ± 1.2 L, P = .02) and body water (from 54.9% to 51.6%, P = .003). A post-Tx increase in body fat mass (from 26% to 30%, P = .003) possibly blunted the beneficial impact of kidney Tx on SA. All parameters remained unchanged in the control group. In conclusion, SA is a frequent condition in ESKD patients and partially improved by kidney Tx. We suggest that SA should be systematically assessed before and after kidney Tx.

ClinicalTrials.gov Identifier: NCT02020642.

KEYWORDS

clinical research/practice, disease pathogenesis, kidney transplantation/nephrology, kidney transplantation: living donor, lung disease

1 | INTRODUCTION

Sleep apnea (SA) is a breathing disorder characterized by intermittent interruptions of respiration, causing recurrent oxygen desaturations during sleep, which results in sleep fragmentation and daytime sleepiness. In addition to its negative consequences on the quality of sleep and life, SA also represents a risk factor for metabolic and cardiovascular diseases.[1] In patients with chronic kidney disease (CKD) the prevalence of SA is high and increases as patients progress toward end-stage kidney disease (ESKD), reaching a prevalence rate of 56.2% for moderate to severe SA in hemodialysis patients.[2,3] This may be explained in part by the increased prevalence both of SA and CKD as individuals get older and by an increasing prevalence of obesity in the general population. However, the association between SA and ESKD persists after correction for potential confounding factors such as diabetes, hypertension, and obesity, supporting a direct association

Abbreviations: AASM, American Academy for Sleep Medicine; AHI, apnea-hypopnea index (per hour of sleep); BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ODI, oxygen desaturation index (per hour of sleep); PSG, polysomnography; SA, sleep apnea; Tx, transplantation; WHR, waist-to-hip ratio.

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between SA and ESKD.[4,5] Fluid overload has been suggested as the main population-specific pathophysiological mechanisms linking SA and ESKD,[6,7] which would add on classical risk factors for SA, such as age, increased body mass index (BMI), or upper airway anatomy.

In a previous study, we provided evidence for overnight rostral fluid shift (ie, nighttime displacement of body water from the lower body parts to the neck) as a causal factor in the pathogenesis of obstructive SA in ESKD patients on intermittent hemodialysis, by demonstrating that a negative fluid balance obtained during hemodialysis can improve the severity of obstructive SA in overhydrated ESKD patients.[8] Kidney transplantation (Tx) restores kidney function and corrects the hydration status of ESKD patients. A previous polysomnographic study reported a SA prevalence of 22% in kidney Tx recipients, which is similar to the prevalence of SA in the general population[9] and lower than that in ESKD patients on hemodialysis.[2,3,5] This observation indirectly suggests a beneficial effect of kidney Tx on SA severity. However, literature on the impact of kidney Tx on SA based on pre- and post-Tx measurements is scarce and inconclusive, consisting of one case report[10] and four small and heterogeneous longitudinal case series studies.[11-14] Overall, these reports included 81 ESKD patients, of whom only 23 presented with moderate to severe (ie, clinically relevant) pre-Tx SA.

The aim of this study was to prospectively assess the impact of kidney Tx on SA severity in ESKD patients with moderate to severe SA. We hypothesized that the improvement in kidney function after Tx and the resulting correction of hydration status may improve SA severity.

2 | PATIENTS AND METHODS

2.1 | Design and patients

This study was conducted at the Transplantation Center of the Lausanne University Hospital, Switzerland. The study complied with the Declaration of Helsinki and was approved by the local institutional ethics committee (Commission Cantonale d'Ethique de la Recherche du canton de Vaud sur l'Etre Humain, Lausanne, institutional review board approval number 157/12). All participants provided written informed consent. The study was registered at ClinicalTrials.gov (Identifier: NCT02020642).

Between September 2013 and May 2017, 196 ESKD adult patients on the kidney Tx waiting list (pre-Tx) were screened for sleep-disordered breathing. Sleep recording was performed using home nocturnal polysomnography (PSG) (see the next section) to measure the apnea-hypopnea index (AHI) per hour of sleep. In hemodialysis patients, PSG was performed on non-dialysis days. At the beginning of each sleep recording, anthropometric parameters were measured and a bioimpedance analysis was performed.

We invited all the study participants with moderate to severe pre-Tx SA (AHI ≥ 15/h) not yet transplanted 6 months after inclusion to undergo a follow-up (pre-Tx FU) visit with PSG and bioimpedance analysis. These patients represented the control group without kidney Tx.

Patients with moderate to severe pre-Tx SA (AHI ≥ 15/h) who underwent kidney Tx were reassessed after 6 months (post-Tx) using the same protocol. Patients were given induction therapy based on their immunological risk (basiliximab or antithymocyte globulin) followed by maintenance immunosuppression consisting of a calcineurin inhibitor (majority on tacrolimus), a mycophenolic acid-based agent and steroids at tapering doses.

2.2 | Sleep recording

Home unattended PSG data were recorded with a digital system device. Certified technicians equipped the subjects with a PSG recorder (Titanium, Embla® Flaga, Reykjavik, Iceland) between 5 PM and 8 PM at the Center for Investigation and Research in Sleep (CIRS, University Hospital of Lausanne, Switzerland). All sleep recordings took place in the patients' home environment in accordance with the American Academy for Sleep Medicine (AASM) 2007 recommended setup specifications.[15] PSG recordings were manually scored using Somnologica software (Version 5.1.1, by Embla®). Sleep stages and arousals were scored according to the AASM 2007 criteria.[16-18] Sleep efficiency was calculated as the percentage of time in bed spent asleep. Chest and abdominal motion bands, finger pulse oximetry, and a nasal pressure cannula were applied to analyze respiration. Respiratory events were scored according to the AASM 2012 consensus criteria[19] by the same sleep center physician (JHR), blinded to patient's identity, transplant status, and anthropometric measures. Apnea was defined as a reduction >90% of airflow and classified as obstructive if thoracic motion was present, or as central in absence of breathing efforts. Hypopnea was defined as a decrease in airflow by 30% associated with either an oxygen desaturation ≥3% or an arousal. Only events lasting ≥10 seconds were considered. Special care was taken to avoid overscoring hypopnea during periodic leg movement periods by only scoring hypopnea if the event was associated with a drop in oxygen saturation. The AHI was calculated as the number of apneas and hypopneas per hour of sleep, and moderate to severe SA was diagnosed when AHI was ≥15/h. The oxygen desaturation index (ODI) was calculated as the number of ≥3% arterial oxygen desaturations per hour of sleep.

In the evening before the PSG recording, patients were asked to complete the Epworth Sleepiness Scale (ESS), a self-administered questionnaire evaluating the risk of falling asleep while engaged in eight different activities. The ESS score can range from 0 to 24. Daytime sleepiness was defined as an ESS score of ≥10.[20]

2.3 | Anthropometric parameters and body composition

Neck circumference was measured above the cricothyroid membrane using a nonstretchable tape with the patient in a sitting position, before PSG recording. Body weight was measured before PSG recording, in light indoor clothing without shoes, using a calibrated Seca® scale. Height was measured to the nearest centimeter using a wall-mounted

stadiometer. BMI was calculated as weight divided by height squared. Waist circumference was measured to the nearest centimeter with a nonstretchable tape with the subject in a standing position, over the unclothed abdomen at the midpoint between the lowest rib and the iliac crest, and hip circumference was measured around the widest portion of the buttocks, as recommended by the World Health Organization (WHO). The waist-hip ratio (WHR) was calculated as the ratio of the circumference of the waist to that of the hips.

Body composition was assessed by multifrequency bioelectrical impedance (Body Composition Monitor®, BCM®; Fresenius Medical Care, Bad Homburg, Germany). Impedance to electric current between two pairs of electrodes, placed at the level of the wrist and the ipsilateral ankle, was used to assess body water and body fat mass, both expressed as absolute values and percentage of body weight. The fluid overload volume was directly provided by the BCM device according to a factory-set algorithm, comparing the measured extracellular water (ECW) to the expected ECW, which is estimated assuming normal hydration of the measured lean tissue and adipose mass. This technique has been validated against the respective gold standards in healthy individuals[21] and in hemodialysis patients,[22] and has shown an excellent reproducibility (coefficient of variation 0.15%-0.64% for the estimation of total body water).[23]

2.4 | Laboratory analysis

Serum creatinine was measured using the Jaffé kinetic compensated method (Roche Diagnostics, Basel, Switzerland). Kidney function was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. CKD stage was defined according to the revised Kidney Disease – Improving Global Outcomes (2012) classification, which includes five stages of estimated glomerular filtration rate (eGFR; stage 1 to stage 5).[24]

2.5 | Statistical analysis

Statistical analysis was conducted using Stata 11.0 for Windows (Stata Corp LP, College Station, TX). Mean and standard deviation (SD) were used to describe continuous variables, and percentages were used to describe dichotomous or categorical variables.

We used an unpaired *t* test or Freeman-Halton extension of Fisher's exact test to compare baselines characteristics of patients and control group.

We used a paired *t* test or McNemar test to compare the measurements performed before and after kidney Tx. We explored the association between the change in AHI after kidney Tx and

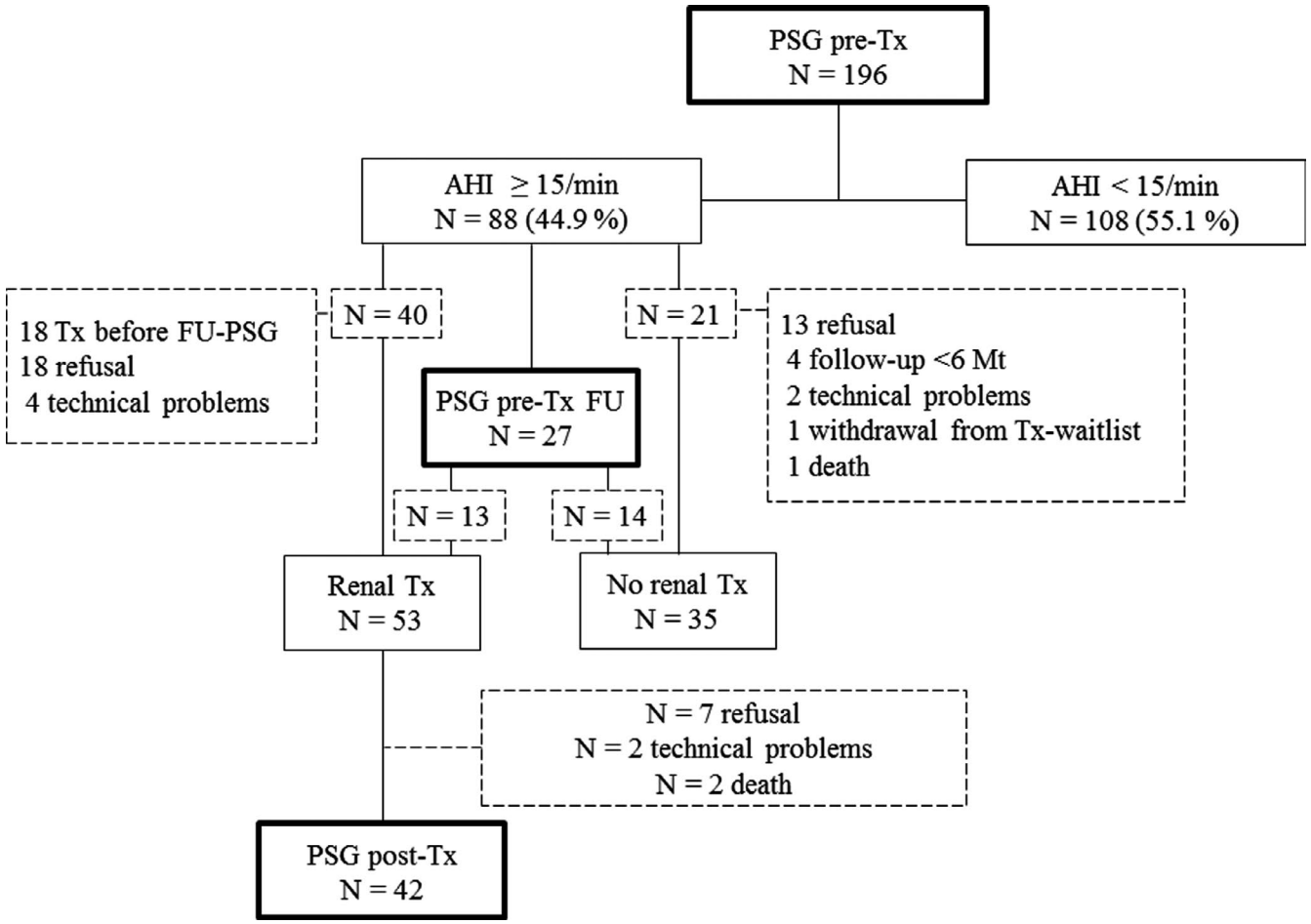

FIGURE 1 Study flowchart. AHI, apnea-hypopnea index; FU, follow-up; PSG, polysomnography; Tx, kidney transplantation

concomitant changes in body composition parameters using linear regression analysis and multivariate linear regression analysis. Multivariate linear regression analysis including age, BMI, neck circumference, and fluid overload as candidate factors were used to search for baseline characteristics predicting the post-Tx amelioration in AHI.

Based on a previous longitudinal study,[11] we calculated that we needed 36 patients with pre- and post-Tx assessments to have 80% power to detect a 50% improvement in the severity of SA (assuming a mean pre-Tx AHI of 20.2 ± 15.1/h), using a paired *t* test and an alpha error of 0.05.

3 | RESULTS

3.1 | Study population

Study flow diagram is shown in Figure 1. Baseline demographic and relevant medical data for the study population and control group are detailed in Table 1. A total of 196 adult ESKD patients waiting for kidney Tx underwent pre-Tx assessment. Of these, 88 (44.9%) were found to have moderate to severe SA, 53 underwent kidney Tx. Forty-two of these patients agreed to complete the post-Tx assessment at 6.4 ± 3.4 months after kidney Tx (17.1 ± 10.7 months after the pre-TX assessment) and were included in the final analysis.

All patients had pre-Tx severe stage 5 kidney failure. Twenty-two patients were treated by in-center intermittent hemodialysis 3 times a week (mean eKt/V 1.51 ± 0.26), 9 patients were treated by peritoneal dialysis (mean Kt/V 1.76 ± 0.21) and 10 patients were not on dialysis treatment (residual kidney function). All patients had an improved kidney function at the time of post-Tx assessment (to stage 1 [n = 3], stage 2 [n = 5], stage 3 [n = 30], or stage 4 [n = 4]). Mean post-Tx eGFR was 48.6 ± 19.6 mL/min/1.73 m^2.

Twenty-seven patients were included in the control group, and were evaluated at baseline and after 6 months later (pre-Tx FU). All control patients had severe stage 5 kidney failure at the time of both baseline and pre-Tx FU assessment. Thirteen patients of the control group were subsequently transplanted and also underwent the post-Tx assessment.

3.2 | PSG, anthropometric, and bioimpedance analysis

Table 2 summarizes the main pre- and post-Tx findings for kidney Tx patients; those of the control group are detailed in Table 3. The main finding was a statistically significant improvement in SA severity after kidney Tx, with the AHI decreasing from 44.2 ± 24.3 to 34.7 ± 20.9/h (*P* = .021); eight patients had a reduction in SA severity from moderate or severe to mild (AHI < 15/h). In contrast, there was a slight, nonsignificant worsening in AHI between the baseline and FU PSG assessment in the control group (from 38.7 ± 23.4 to 44.9 ± 28.2/h, *P* = .217). The change in AHI after kidney Tx was significantly different when compared to the control group (−9.5 ± 25.7 vs +6.2 ± 25.5/h, *P* = .015) (Figure 2). The between-group difference in AHI remained significant after exclusion of outliers (*P* = .007).

Among baseline characteristics, only the amount of fluid overload was predictive of the post-Tx improvement in AHI (*P* = .027) in multivariate linear regression analysis, whereas classical risk factors for SA (such as BMI, age, and neck circumference) were not significantly associated with the post-Tx change in AHI.

There was a significant reduction in total body water and fluid overload volume from before to after Tx in kidney Tx recipients, whereas fat mass, neck circumference, and WHR increased (Table 2). No changes in anthropometric and bioimpedance parameters were observed in the control group (Table 3). Linear regression analysis confirmed a significant association between the change in AHI and the change in fluid overload volume (*P* = .002) from pre- to post-Tx (Figure 3).

The changes in total body water and body fat were not significantly association with the post-Tx change in AHI when analyzed separately in linear regression, whereas considering these parameters together in a multivariate linear regression model, both the

TABLE 1 Baseline characteristics of kidney transplant recipients and the control group

Characteristic	Kidney Tx (n = 42)	Control group (n = 27)	*P* value
Age, years, mean (SD)	56.6 (9.7)	56.0 (8.6)	.792
Male, n (%)	33 (78.6)	22 (81.5)	.769
Body mass index, kg/m^2, mean (SD)	28.1 (4.2)	31.1 (5.1)	.011
Ethnicity, n (%)			
Caucasian	35 (83.3)	23 (85.2)	1.00
Asian	3 (7.1)	2 (7.4)	
African	4 (9.5)	2 (7.4)	
Disease history, n (%)			
Hypertension	38 (90.5)	25 (92.6)	.761
Diabetes	12 (28.6)	11 (40.7)	.295
Renal disease			
Diabetic/ hypertensive	16 (38.1)	10 (38.5)	.596
Glomerulonephritis	9 (21.4)	6 (23.1)	
ADPKD	9 (21.4)	3 (11.5)	
Reflux disease	4 (9.5)	2 (7.7)	
Other/unknown	4 (9.5)	6 (19.2)	
Renal replacement therapy, n (%)			
Hemodialysis	22 (52.4)	12 (46.2)	.850
Peritoneal dialysis	9 (21.4)	6 (23.1)	
ESKD without RRT	11 (26.2)	8 (30.7)	

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ESKD, end-stage kidney disease; RRT, renal replacement therapy; SD, standard deviation; Tx, transplantation.

TABLE 2 Changes in polysomnography parameters, anthropometric data, and bioimpedance analysis after kidney transplantation

	Pre-Tx (n = 42)	Post-Tx (n = 42)	*P* value
Sleep-disordered breathing			
AHI/h, mean (SD)	44.2 (24.3)	34.7 (20.9)	.021
ODI/h, mean (SD)	45.2 (26.0)	38.4 (22.9)	.107
OAI/h, mean (SD)	9.3 (14.4)	7.6 (10.5)	.400
CAI/h, mean (SD)	4.4 (14.4)	1.9 (4.4)	.278
Daytime sleepiness[a], n (%)	14 (33.3)	13 (30.9)	1.00
Total sleep time, min, mean (SD)	368 (108)	371 (70)	.857
Sleep efficiency, %, mean (SD)	76.1 (16.4)	79.7 (111.8)	.188
Unrefreshing sleep, n (%)	12 (28.6)	10 (23.8)	.687
Anthropometric parameters			
Body mass index, kg/m^2, mean (SD)	28.1 (4.2)	28.6 (4.5)	.106
Waist-hip ratio, mean (SD)	1.02 (0.10)	1.06 (0.12)	.005
Neck circumference, cm, mean (SD)	39.2 (3.4)	39.6 (3.3)	.029
Bioimpedance analysis			
Body water, kg, mean (SD)	44.5 (8.3)	42.5 (7.4)	.007
Body water, % body weight, mean (SD)	54.9 (8.9)	51.6 (7.3)	.003
Fat mass, kg, mean (SD)	21.8 (9.3)	25.4 (11.6)	.002
Fat mass, % body weight, mean (SD)	26.0 (8.8)	29.8 (10.4)	.003
Fluid overload, kg, mean(SD)	1.8 (2.0)	1.2 (1.2)	.020
Medications, n (%)			
Prednisone	6 (14.3)	42 (100.0)	<.0001
Sleep medications	2 (4.8)	2 (4.8)	1.00

Abbreviations: AHI, apnea-hypopnea index; CAI, central apnea index; OAI, obstructive apnea index; ODI, oxygen desaturation index; SD, standard deviation; Tx, kidney transplantation.

[a]Daytime sleepiness was defined as an Epworth Sleepiness Scale score of ≥10.

changes in total body water (*P* = .028) and body fat (*P* = .036) were significantly associated with the post-Tx change in AHI.

4 | DISCUSSION

This study represents the largest available prospective study investigating the impact of kidney Tx on SA severity in ESKD patients with a pre-post study design, and is the first investigating potential causal mechanisms using body composition analysis.

We found a statistically significant improvement in the severity of SA after kidney Tx with a concomitant reduction in body water and a positive correlation between the reduction of fluid overload and the improvement in AHI with kidney Tx, supporting our hypothesis that fluid overload plays a role in the pathogenesis of SA in ESKD patients. Furthermore, fluid overload before Tx was the only predictor of the post-Tx improvement in SA severity. However, the reduction in SA severity was only partial, being blunted by the increase in body fat mass and WHR.

The screening phase of our study represents the largest cohort of ESKD patients on a kidney transplant waiting list studied by full PSG (n = 196). It shows a remarkably high prevalence of moderate to severe SA in this population (44.9%), consistent with the figures obtained in patients on dialysis.[5] Our data add new insights to the existing evidence from previous observational and interventional studies, which identified fluid overload as a population-specific pathophysiological mechanism of SA in ESKD patients, promoting SA through the so-called "overnight rostral fluid shift."[6,7,25,26] Accordingly, the negative fluid balance obtained by hemodialysis has been shown to decrease the severity of SA in overhydrated ESKD patients,[8] even in the absence of any change of the uremic and acid-base status.[26] Kidney Tx represents the most efficient way to restore kidney function, allowing better regulation of fluid status. As a result, SA severity is expected to improve after kidney Tx.

The results of longitudinal studies investigating the impact of kidney Tx on SA severity are inconsistent.[10-14,27] Our results are similar to those from two previous studies, by Jurado-Gamez et al[12] and Mahajan et al[14] The first showed an improvement in mean AHI from 10.0 to 4.9/h in nine patients at 5 months after kidney Tx. Of note, two of the three patients with a pre-Tx AHI ≥ 15/h had resolution of SA after Tx.[12] The second study reported an improvement in median AHI from 1.2 to 0.4/h in 18 young patients undergoing living donor kidney Tx; the three patients with a pre-Tx AHI ≥ 15/h had a decrease in the AHI to <5/h after Tx.[14] In contrast with our observation, Beecroft et al[11] did not find any significant improvement in SA severity after kidney Tx in a cohort of 18 patients (11

TABLE 3 Polysomnography parameters, anthropometric data, and bioimpedance analysis at baseline and follow-up in the control group

	Baseline (n = 27)	Follow-up (n = 27)	*P* value
Sleep-disordered breathing			
AHI/h, mean (SD)	38.7 (23.4)	44.9 (28.2)	.217
ODI/h, mean (SD)	42.1 (4.5)	49.7 (5.2)	.090
Daytime sleepiness[a], n (%)	10 (37.0)	10 (37.0)	1.00
Total sleep time, min, mean (SD)	371.1 (65.4)	347.8 (98.7)	.244
Sleep efficiency, %, mean (SD)	77.7 (9.7)	77.0 (14.4)	.818
Unrefreshing sleep, n (%)	6 (22.2)	6 (22.2)	1.00
Anthropometric parameters			
Body mass index, kg/m^2, mean (SD)	31.1 (5.1)	31.3 (4.9)	.493
Waist-hip ratio, mean (SD)	1.05 (0.10)	1.07 (0.89)	.078
Neck circumference, cm, mean (SD)	41.1 (3.2)	41.1 (3.1)	.872
Bioimpedance analysis			
Body water, kg, mean (SD)	45.8 (6.6)	46.9 (8.4)	.344
Body water, % body weight, mean (SD)	52.1 (8.0)	53.4 (2.3)	.370
Fat mass, kg, mean (SD)	29.4 (11.5)	29.0 (9.3)	.730
Fat mass, % body weight, mean (SD)	31.7 (8.5)	31.5 (6.8)	.830
Fluid overload, kg, mean(SD)	1.7 (1.8)	1.7 (2.1)	.895
Medications, n (%)			
Prednisone	3 (11.1)	3 (11.1)	1.00
Sleep medications	3 (11.1)	3 (11.1)	1.00

Abbreviations: AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SD, standard deviation; Tx, kidney transplantation.

[a]Daytime sleepiness was defined as an Epworth Sleepiness Scale score of ≥10.

with moderate to severe SA). Similarly, Rodrigues et al[13] found no global benefit of kidney Tx on SA severity in a population of 34 ESKD patients. However, in the subgroup of nine patients with AHI > 5/h (four of whom had an AHI > 15/h), AHI decreased from 15.4 to 4.4/h post-Tx and eight of these nine patients showed an improvement in SA severity.[13] Compared with our study, the patients enrolled in both negative studies showed a much larger increase in the post-Tx BMI, which could have masked any positive effects of kidney Tx on SA severity.

In our population, body composition analysis showed a significant increase in body fat mass, despite a stable BMI. Significant increases in the WHR and neck circumference were also observed, possibly as a consequence of post-Tx corticosteroid treatment, improved appetite, fewer dietary restrictions, and limited physical activity. Systemic corticosteroids are widely used, at least during the first year after kidney Tx, and may promote truncular "cushingoid" redistribution of body fat, located on the face and nuchal, truncal, and visceral areas, as shown by the increase in WHR and neck circumference after Tx. This distribution of fat deposits, and particularly the accumulation of fat tissues in the cervical region, can contribute to upper airway collapsibility and thus promote obstructive SA. In fact, SA has been described as being related to Cushing's disease, where excessive corticosteroid use plays a pivotal role.[28]

Our study, which shows some beneficial effect of kidney Tx on SA severity, has several strengths when compared to the existing literature. First, we investigated a substantial population of patients from the kidney Tx waiting list using gold standard PSG and selected only those with moderate to severe pre-Tx SA (ie, a clinically relevant sleep-related breathing disorder). Furthermore, we compared transplanted patients with a similar group of patients on the waiting list who did not undergo Tx. Thus, we could reliably say that differences observed after Tx are attributable to the Tx procedure rather than to the natural evolution of the disease over time. Although intervention and control participants were not randomized, this likely represents the best possible design, because it is not ethical to randomize patients to undergo kidney Tx. The control group population had a significantly higher BMI. However, we do not believe that this would have influenced the different time course of SA severity observed in this population compared with the intervention group because BMI remained stable between the baseline and the follow-up assessment.

Thanks to the prospective design and the bioimpedance analysis, we have obtained direct insights into some of the mechanisms implicated in the improvement in SA severity following kidney Tx, supporting the pathogenetic role of fluid overload in the development of SA in ESKD patients. The bioimpedance assessment allowed confirmation of an increase in body fat mass in the post-Tx period, which can act as a confounder in the evaluation of the net effect of kidney Tx on SA severity (ie, by reducing the positive effect of restoring normovolemia).

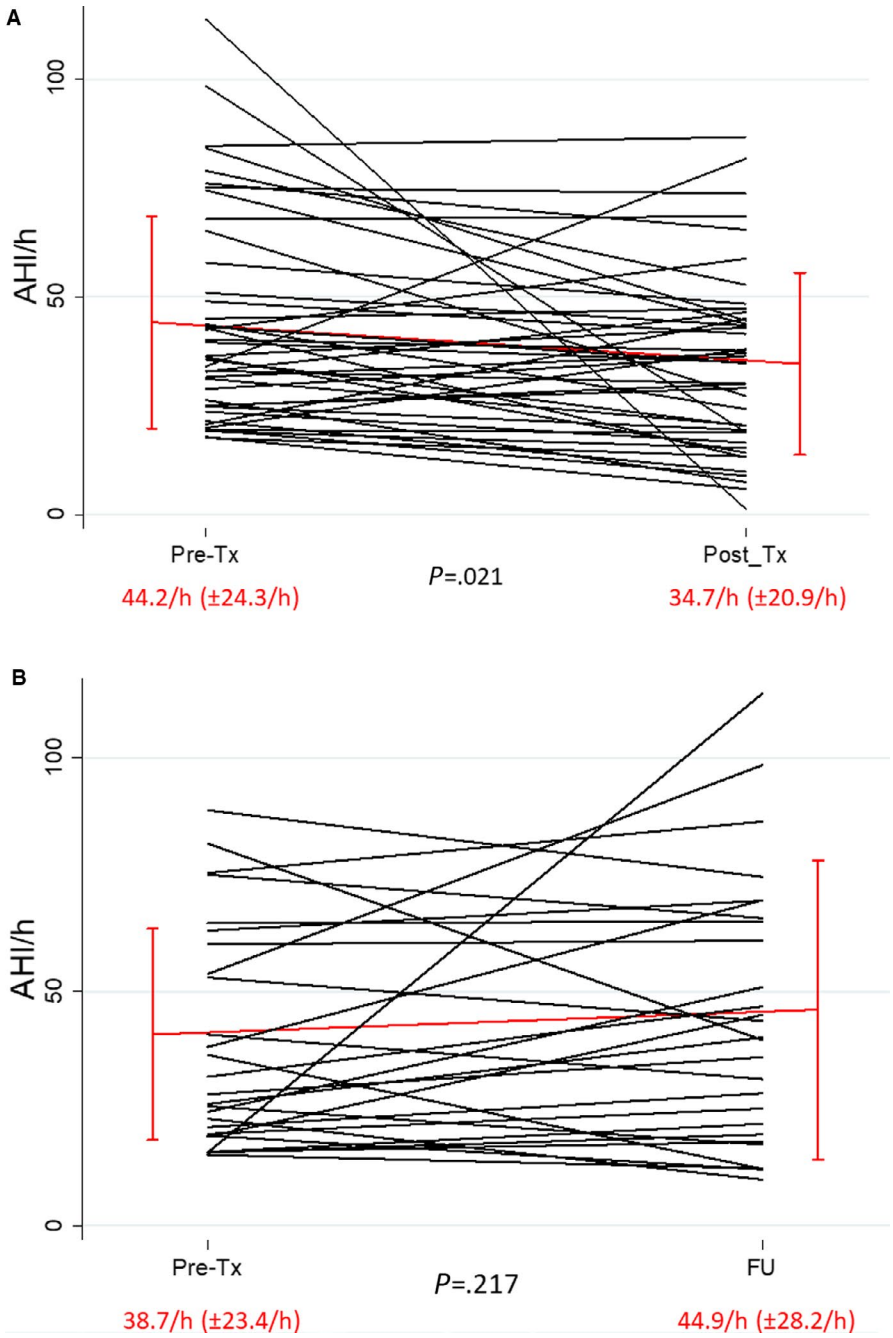

FIGURE 2 Sleep apnea severity: (A) before (pre-Tx) and after (post-Tx) kidney transplantation in the study group; (B) at baseline (pre-Tx) and follow-up (FU) in the control group (without transplantation). AHI, apnea-hypopnea index; FU, follow-up; Tx, kidney transplantation [Color figure can be viewed at wileyonlinelibrary.com]

Kidney Tx is a complex intervention that goes far beyond normalization of the hydration status, also correcting uremia and metabolic acidosis and restoring the impaired synthesis of some endocrine renal factors associated with ESKD. The design of our study did not allow us to determine the relative contributions of restoring fluid balance, improving uremic control, and equilibrating the acid-base status to attenuating SA severity. However, Lyons et al previously demonstrated that fluid removal by ultrafiltration improves SA in ESKD patients, in the absence of any changes in uremic and acid-base status.[26] All the patients were also treated with immunosuppressive agents after Tx, compared with only a few before Tx, but a role of immunosuppressive therapy in the observed amelioration of SA seems unlikely, in the absence of previous scientific evidence or of a pathophysiological rationale supporting a direct relationship.

There are also a few limitations in our study. First, we chose to perform follow-up evaluation at 6 months after Tx, and we cannot determine the long-term impact of kidney Tx on SA. The balance between the positive effects of kidney Tx on fluid and metabolic status and the negative effects of fat redistribution probably varies with the time elapsed since Tx and the cumulative dose of steroids. It is therefore possible that the severity of SA further evolves beyond 6 months after kidney Tx. Another limitation results from the inclusion of patients with existing ESKD at the time of SA diagnosis. Thus, it is not possible to confirm that ESKD was the main causative factor of SA in all studied patients before Tx. A supplementary

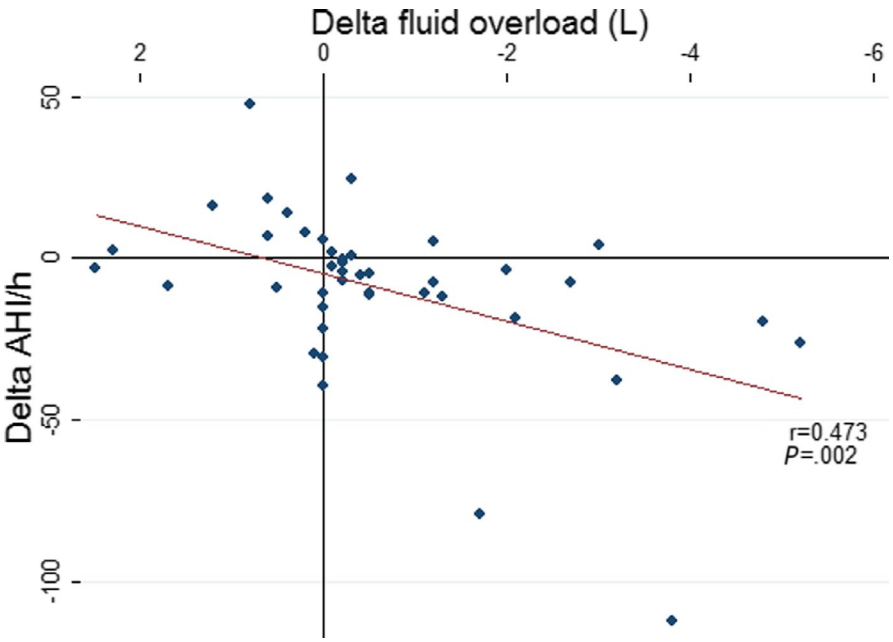

FIGURE 3 Correlation of the change in fluid overload after kidney transplantation ("Delta fluid overload," measured by bioimpedance) with the change in the severity of sleep apnea (Delta AHI). AHI, apnea-hypopnea index [Color figure can be viewed at wileyonlinelibrary.com]

(post-hoc) analysis of our data showed no difference in the SA severity before and after kidney Tx in obese patients (BMI ≥ 30 kg/m^2), suggesting that a subgroup of our patients probably had a "classical" obesity-associated SA, independently from ESKD-specific mechanisms. Intuitively, kidney Tx would have less effect on SA in these patients, which may also be a reason why we observed only a partial AHI improvement after kidney Tx. Finally, we observed no significant change in the prevalence of daytime sleepiness after Tx (as assessed by the Epworth Sleepiness Scale score). However, it should be noted that previous studies performed both in the ESKD population as well as in the general population showed no correlation between daytime sleepiness and severity of SA.[3,5,29]

Overall, kidney Tx appears to have some positive effect on SA severity, probably by restoring kidney function and reducing overhydration, a factor involved in the pathogenesis of SA in ESKD patients. In parallel, transplant patients showed an increase in body fat mass, which probably reduced the magnitude of the post-Tx improvement in SA. Overall, these results suggest that patients scheduled for kidney Tx should be assessed for the presence of SA because this is a frequent condition with a deleterious impact on cardiovascular morbidity and quality of life.[1] SA is also an independent risk factor for postoperative hypoxemia, intensive care unit transfers, and prolonged hospital stay.[30,31] Given the high cardiovascular risk of transplant patients,[32] SA patients should be reassessed after Tx to monitor the evolution of the disease and adapt the therapeutic strategy, if necessary. It is possible that avoiding weight gain, for example through dietary or counseling measures, may optimize the beneficial effect of kidney Tx on SA severity.

In conclusion, SA is a frequent condition in ESKD patients and is only partially improved by kidney Tx. We suggest that the severity of SA should be systematically assessed before and after kidney Tx.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

AUTHOR CONTRIBUTIONS

VFO, AO, JHR, MB, MP and RH: designed the experiment; VFO, AO, JHR, GN, JPV, DG, MM, MP and RH: conducted the research; VFO, AO, JHR and RH: analyzed the data and performed the statistical analyses; VFO, AO, JHR, MB and RH: wrote the manuscript; VFO, AO and RH: have primary responsibility for the final content. All authors had full access to all of the data (including statistical reports and tables) in the study, revised the manuscript for important intellectual content and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, VFO, upon reasonable request.

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