OPEN

Does Kidney Transplantation Affect Sleep and Fatigue in Patients With Kidney Disease?

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Background. Sleep disorders and fatigue are highly prevalent in chronic kidney disease (CKD) and end-stage kidney disease (ESKD) patients but there is limited evidence on the effect of kidney transplant (KTx) on these. **Methods.** In a prospective cohort study of patients with advanced CKD (estimated glomerular filtration rate<30 mL/min/1.73 m^2) or ESKD, polysomnography and patient-reported symptom assessments were conducted. Pre- and post-KTx changes in sleep apnea (SA) severity (measured by apnea hypopnea index [AHI]) were analyzed and compared with patients who did not receive KTx. Regression models were used to examine predictors of SA severity. **Results.** Among 77 patients (mean age 51 y, BMI 29 kg/m^2, 66% males, 23% ESKD), 61% had SA at baseline. Among 39 KTx recipients, 56% had SA, with 39% having moderate-severe SA after 10 ± 5.6 months post-KTx. There was no difference in AHI in either the KTx (median 6 versus 8; $P = 0.37$) or no-KTx (median 15 versus 16; $P = 0.61$) groups after an average of 19.9 ± 8.9 months. KTx led to significant clinically meaningful improvements in fatigue and health-related quality of life (adjusted effect size 0.3–0.6). In multivariable regression, baseline AHI was the only significant predictor of SA severity (adjusted β = 3.6/5 units, 95% confidence interval 2.1, 5.2) after adjusting for KTx status, age, sex, and body mass index. **Conclusions.** More than half of the KTx recipients had SA. There was no significant change in SA severity with KTx. Clinically meaningful moderate size improvements in patient-reported fatigue and health-related quality of life may be seen with KTx.

(*Transplantation Direct* 2019;5: e461; doi: 10.1097/TXD.0000000000000895. Published online 29 May, 2019.)

INTRODUCTION

Sleep disorders and fatigue are common in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) on renal replacement therapy (RRT). Sleep-disordered breathing (SDB) affects around 17%–34% of the general population,[1] whereas the prevalence is reported to be around 10%–50% in ESKD patients.[2] Similarly, the prevalence of fatigue is as high as 84% in CKD stage 5 and 60%–97% in patients on long-term RRT.[3,4] SDB, excessive daytime sleepiness, and fatigue are not only associated with poor health-related quality of life (HRQOL) but also may be associated with increased morbidity and mortality, as in the general population.[5-8]

Received 8 March 2019.

Accepted 15 March 2019.

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M.J. was supported by NIDDK P30 DK079307, AHA 11FTF7520014, and R01DK114085; M.U. was supported by NIH K23DK66006 and R01DK77785; S.R.P. was supported by American Sleep Foundation, Bayer Pharmaceuticals, and Philips Respironics and has received personal consulting fees from the American Academy of Sleep Medicine. The other authors declare no conflicts of interest.

This study was presented in a poster at the National Kidney Foundation Spring Clinical meetings; April 2018; Austin, TX.

The authors declare no conflicts of interest.

S.T. participated in data analysis and writing of the article. S.H. participated in statistical data analysis. J.Y. participated in statistical data analysis. X.R. participated in statistical data analysis. M.F. participated in data collection and management. P.S. participated in research design and conduct of the research. S.R.P. participated in data analysis and writing of the article. M.U. participated in research design, conduct of the research, data analysis, and writing of the article. M.J. participated in research design, conduct of the research, data analysis, and writing of the article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000895

In patients with CKD/ESKD, possible mechanisms for obstructive sleep apnea (OSA), the most common form of SDB, may include fluid overload and subsequent upper airway edema, leading to dynamic airway obstruction[2,9,10] and perhaps uremia-related factors.[2] Moreover, fluid overload and an enhanced sensitivity to hypercapnia have also been suggested as possible mechanisms for another form of SDB, Cheyne-Stokes respiration-central sleep apnea (CSA), in these patients.[11] The mechanism of fatigue in these patients is multifactorial including increased prevalence of SDB, restless legs, excessive daytime sleepiness, uremia-related factors, depressive symptoms, cardiovascular disease, hypoalbuminemia, anemia, benzodiazepine use, etc.[5,6,12,13]

The role of kidney transplant (KTx) in improving SDB and fatigue in these patients is unclear. KTx may improve SDB by mitigating the fluid overload and uremia-related factors. It may improve fatigue as well, given the independence from dialysis, allowing for an increase in physical mobility, improvement in quality of life, resolution of uremic symptoms, increase in appetite, and improvement in sleep quality. A few small case studies and prospective studies studying SDB have shown conflicting results[2,14-16] which are limited by sample size, select patient populations, and short post-Tx follow-up period. We are not aware of any study that has examined longitudinal changes in fatigue after KTx.

The aim of our study was as follows: (a) to evaluate the prevalence of SDB in patients with KTx, and (b) to examine changes in patient-reported outcomes of sleep quality and fatigue, and polysomnography (PSG) measures of sleep quality in KTx patients. To our knowledge, this is the first study to assess longitudinal changes in these outcomes among patients who received KTx in comparison to a control CKD stages 4 and 5 or ESKD population who did not. We hypothesized that KTx would have a positive impact on both PSG and patient-reported outcomes.

MATERIALS AND METHODS

Study Participants

The study cohort used for our study was derived from a prospective cohort study enrolling patients from outpatient nephrology clinics, local dialysis centers, and kidney transplantation clinics in Western Pennsylvania between March 2004 and December 2008.[9] Inclusion criteria included all patients who were aged >18 years with advanced CKD (estimated glomerular filtration rate calculated per Modification of Diet in Renal Disease ≤30 mL/min/1.73 m^2), and who had in-home PSG studies done on 2 separate occasions. For patients who underwent a KTx, a PSG before and after KTx was required to be included in the study. Exclusion criteria included patients of age >90 years, acute medical or psychiatric illness, active alcohol abuse, and patients who did not have 2 in-home PSG studies during the course of the study. Patients were divided into 2 groups—those who underwent KTx and those who did not undergo KTx (No-KTx). The study was approved by the University of Pittsburgh Institutional Review Board, and all patients provided informed consent.

Clinical and Demographic Data Collection

Baseline data collection was done with the help of a standardized health interview and included sociodemographics, comorbidities such as cardiovascular diseases, diabetes, hypertension and stroke, and medications used including immunosuppressants and antidepressants. Clinical (blood pressure and body mass index [BMI]) and laboratory data were collected from medical charts.

Outcomes Assessment

All patients included in this analysis completed objective and subjective data collection at 2 time points—baseline (T1) and follow-up (T2). For patients who underwent a KTx, baseline (T1) parameters were collected before the KTx and follow-up (T2) parameters were collected after KTx. The timing of follow-up was at least 6 months post-KTx to permit a stable immunosuppression regimen and kidney function in the KTx group.

Assessment of Sleep With PSG

Unattended in-home PSG was used for objective assessment of sleep quality and presence of obstructive, central, or mixed sleep apnea. Ambulatory Siesta monitor (Charlotte, NC) was used to record PSG data at habitual sleep times for 1 night. The apparatus included bilateral central and occipital electroencephalogram channels, bilateral electro-oculogram, and bipolar submentalis electromyogram, along with bipolar electrocardiogram for heart rate and position sensors for body position monitoring. Other monitoring included inductance plethysmography to measure abdominal and thoracic effort, pulse oximetry (Nonin, Minneapolis, MN) to measure oxyhemoglobin saturation, nasal-oral thermocouple and nasal pressure to measure airflow, and arm and leg electromyograms to measure periodic leg movements. Recorded data were analyzed by trained PSG technologists, who were blinded to patient's renal function or KTx status. Respiratory events were scored using 1999 American Academy of Sleep Medicine criteria for apneas and hypopneas.[17]

The PSG outcome variables of interest were apnea hypopnea index (AHI), total sleep time (TST; sleep time excluding periods of wakefulness during the night), %TST with oxyhemoglobin saturation under 90%, sleep latency, wakefulness after sleep onset (WASO), percent Stage N1 sleep, percent Stage N2 sleep, percent Stage N3 (slow wave) sleep, percent Stage R sleep, and periodic leg movement index (PLMI). AHI was used to classify SDB severity as none (<5 per h), mild (5–14 per h), moderate (15–29 per h), and severe (≥30 per h). The obstructive apnea index (OAI) was calculated as the number of obstructive apneas per hour of TST. The central apnea index (CAI) was calculated as the number of central and mixed apneas per hour of TST.

Patient-reported Sleep Outcomes

Sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI), a 19-item questionnaire exploring global sleep quality over the previous month with higher scores reflecting worse quality.[18]

Participants were also asked to complete the Epworth Sleepiness Scale (ESS), an 8-item questionnaire assessing the likelihood of falling asleep in specific situations with a score ≥10 indicating excessive daytime sleepiness.[19]

Lastly, the Hopkins Restless Legs Syndrome (RLS) Diagnostic Questionnaire, which included 9 questions relating to diagnosis of RLS, was also asked to be filled, and patients were classified as having or not having RLS, based on the response criteria.[20]

Patient-reported Fatigue Outcome

Fatigue was assessed using the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, which was scored from 0 to 52, with a higher score indicating lower levels of fatigue with an assessment of fatigue over 7 days using 5-point Likert scale ranging from "Not at all" to "Very much." The scale encompasses physical, functional, emotional, and social aspects of fatigue.[21,22] This scale has excellent internal consistency, test–retest reliability, and has been validated in many populations including the general US population, and many chronic disease including kidney disease patients.[22,23]

Other Patient-reported Outcomes

The 36-item short-form questionnaire (SF-36) was used to assess the HRQOL. It is composed of the mental component score (MCS) assessing vitality, social functioning, role limitations due to emotional problems and emotional well-being, and the physical component score (PCS) assessing physical health problems, bodily pain, general health and role limitations due to physical problems.[24,25] It is scored from 0 to 100, with higher scores indicating higher quality of life.[26]

Statistical Analysis

Categorical and continuous variables were presented using frequencies with percentages and means with SD (or medians with interquartile range for skewed distributions), respectively. Between-group comparisons were conducted using *t*- and χ^2 tests or Fisher exact test, depending on the variable type. Wilcoxon rank-sum test was used for highly skewed, continuous data. KTx and No-KTx groups were compared for baseline characteristics and duration between time points of PSG assessments. Within-group changes over time were assessed using paired *t*-test or Wilcoxon signed-rank test for continuous outcomes; the McNemar test was used for restless legs syndrome. We also evaluated whether changes in PSG measures from baseline (T1) to follow-up (T2) differed between the 2 groups using 2-sample *t*-test or Wilcoxon rank sum test for continuous variables. Unadjusted and adjusted median regression models were used to examine the association between transplant receipt and changes in AHI. For outcomes that are fairly symmetric, ordinary linear regression models were used. Covariates used for adjustment were baseline AHI, gender, BMI, and age. These covariates were chosen based on clinical rather than statistical reasons and considering the limited sample size. Model assumptions were assessed using standard residual analysis. Effect sizes were calculated based on standardized regression coefficients using the baseline SD as scaling factor. Given the limited power in our study, we performed a meta-analysis pooling data from our study and the 3 prior studies that have looked at pre and post-KTx AHI changes.[14-16] The summary of data from these studies is in Table S1 (**SDC,** http://links.lww.com/TXD/A208).

All statistical analyses were carried out in R (version 3.5.1)[27] using the dplyr package[28] for data manipulation, compareGroups[29] for descriptive tables, and ggplot2[30] for graphics.

RESULTS

Baseline Characteristics

Among 203 patients initially enrolled in the study, 119 completed baseline PSG and 77 completed the second PSG. Reasons for drop-out included patients not interested (23), loss to follow-up (34), deceased (16), poor health (14), and other reasons (56). Among the 77 patients (77% advanced CKD and 23% ESKD), 39 had a KTx (Table 1). There were no significant differences in age, gender, race, or other sociodemographic characteristics between the KTx and No-KTx groups. There were no significant differences in the proportion of CKD or ESKD patients in both groups and the dialysis vintage. The average baseline eGFR in CKD patients was 16.7 versus 22.0 mL/min/1.73 m^2 for KTx and No-KTx group, respectively ($P < 0.01$). Comorbidity burden including cardiovascular disease, hypertension, stroke, and renal disease was similar in both groups, except that there were fewer diabetics in the KTx group compared to the No-KTx group (25.6% versus 54.1%; $P = 0.02$).

The KTx group had a lower BMI compared to the No-KTx group at the time of their first PSG (T1) (26.7 versus 30.5 kg/m^2; $P = 0.005$), but both groups had similar BMI at the time of second PSG (T2). There was no statistical difference between the groups in terms of baseline immunosuppressive medications, antidepressants, benzodiazepines, sedatives, or laboratory parameters.

PSG Sleep Measures at Baseline (T1)

At baseline, 61% of all patients had sleep apnea and 44% had moderate-severe sleep apnea, and this was similar in both the groups ($P = 0.12$ and 0.21, respectively). At baseline, 43% of the CKD and 50% of the ESKD patients had moderate-severe sleep apnea. The median (Q1, Q3) AHI for the whole cohort was 8.9 (3.4, 25.9) and similar in the KTx and No-KTx groups ($P = 0.06$). The baseline PSG variables in both the groups were similar except for longer sleep duration (TST 387 versus 333 min; $P = 0.04$) and greater proportion of slow wave sleep time (8.6% versus 5.1%; $P = 0.01$) in the KTx group (Table 2).

Changes in PSG Measures in KTx and No-KTx Group

The mean time difference between the two PSGs was 19.9 ± 8.9 months (18.6 ± 8.9 mo in KTx and 21.2 ± 8.8 mo in No-KTx group; $P = 0.19$). In the KTx group, the mean time between the KTx and second PSG was 10.0 ± 5.6 months.

Among patients who received KTx, 56% had sleep apnea and 39% of the patients had moderate-severe sleep apnea. The median (Q1, Q3) post-KTx AHI was 7.7 (3.0, 20.5). There was no significant difference in sleep apnea severity after KTx—the median (Q1, Q3) post minus pre AHI was 1.6 (–2.3, 3.7) $P = 0.37$ (Figure 1). Patients spent significantly less time in Stage N1 sleep after KTx compared to pre-KTx (12.2% versus 8.7% of TST; $P = 0.002$). There was no difference in any of the other PSG variables.

In patients who did not receive KTx, 57% had moderate-severe sleep apnea at the time of second PSG, and the median (Q1, Q3) AHI was 16.2 (5.5, 21.0), which was not significantly different from the AHI at the time of first PSG ($P = 0.62$). At the follow-up PSG (T2) in the No-KTx patients, the proportion of Stage N1 sleep was lower (median 5.5% versus 8.8% of TST; $P = 0.003$) and proportion of Stage N2 sleep was greater (median 66.1% versus 60.2% of TST; $P = 0.04$) when compared to the first PSG. Changes in other PSG variables were not statistically significant (**Table S2, SDC,** http://links.lww.com/TXD/A208).

Comparison of Longitudinal Changes in PSG in KTx and No-KTx Group

Longitudinal changes in PSG variables in the KTx and No-KTx groups are compared in Table 3. Overall, there was

TABLE 1.

Characteristics of the study cohort

	All patients, N = 77	Kidney transplant group, n = 39	No kidney transplant group, n = 38	*P*
Age, y	50.7 (13.3%)	48 (13.8%)	53.4 (12.3%)	0.07
Male	51 (66.2%)	28 (71.8%)	23 (60.5%)	0.42
Race				0.09
White	56 (72.7%)	32 (82.1%)	24 (63.2%)	
Black	19 (24.7%)	7 (17.9%)	12 (31.6%)	
Asian/Pacific	2 (2.6%)	0 (0%)	2 (5.3%)	
High school graduate or more	71 (92.2%)	38 (97.4%)	33 (86.8%)	0.11
Married	47 (61.0%)	26 (66.7%)	21 (55.3%)	0.49
Employed	32 (41.6%)	18 (46.2%)	14 (36.8%)	0.55
Ever smoker	34 (47.2%)	18 (50.0%)	16 (44.4%)	0.81
Cardiovascular disease	13 (17.1%)	4 (10.3%)	9 (24.3%)	0.19
Diabetes	30 (39.5%)	10 (25.6%)	20 (54.1%)	0.02
Stroke	4 (5.3%)	1 (2.6%)	3 (8.1%)	0.36
Hypertension	66 (90.4%)	36 (92.3%)	30 (88.2%)	0.70
Renal disease				0.20
CKD	59 (76.6%)	27 (69.2%)	32 (84.2%)	
ESKD	18 (23.4%)	12 (30.8%)	6 (15.8%)	
Systolic BP, mm Hg	146 (23.4)	147 (19.4)	145 (27.4)	0.73
Diastolic BP, mm Hg	83.2 (13.6)	85.2 (12.9)	81 (14.3)	0.20
BMI at first PSG, kg/m^2	28.6 (5.7)	26.7 (4.3)	30.5 (6.5)	<0.01
BMI at second PSG, kg/m^2	29.4 (7.1)	28.9 (8.3)	29.9 (6.0)	0.60
Change in BMI between PSGs (T2–T1), kg/m^2	0.8 (5.6)	2.1 (7.1)	-0.6 (3.1)	0.05
Dialysis vintage, months	12 (0, 21)	12 (0, 15)	6 (0, 21)	0.73
PSG on day of hemodialysis				0.64
Yes	8 (44.4%)	6 (50%)	2 (33.3%)	
No	10 (55.6%)	6 (50%)	4 (66.7%)	
Sedatives	6 (7.8%)	3 (7.7%)	3 (7.9%)	1.00
Antidepressants	11 (14.3%)	7 (17.9%)	4 (10.5%)	0.55
Steroids	7 (9.1%)	4 (10.3%)	3 (7.9%)	1.00
Immunosuppressants	10 (13.0%)	5 (12.8%)	5 (13.2%)	1.00
Tacrolimus	9 (11.7%)	3 (7.7%)	6 (15.8%)	0.31
Albumin, g/dL	3.9 (0.6)	3.9 (0.5)	3.8 (0.8)	0.58
Parathyroid, pg/mL	339 (411)	383 (496)	294 (348)	0.73
Hemoglobin, g/dL	11.7 (1.9)	11.8 (2.2)	11.6 (1.5)	0.69
Phosphorus, mg/dL	4.6 (1.0)	4.7 (0.9)	4.5 (1.1)	0.80
Bicarbonate, mEq/L	24.7 (3.2)	24.8 (2.5)	24.6 (4.1)	0.87
Baseline creatinine, mg/dL	5.3 (2.7)	6.0 (3.0)	4.2 (1.9)	0.04
Baseline eGFR, mL/min/1.73 m^2 (only for CKD group)	19.4 (7.0)	16.7 (5.3)	22.0 (7.6)	<0.01
Cr at follow-up (only for the KTx group)	–	1.7 (0.8)	–	–

Table shows mean (SD) or median (quartile 1, quartile 3) or frequency (%). *P* values were based on two-sample *t*-test or Wilcoxon rank sum test for continuous variables and χ^2 or Fisher exact test for categorical variables.

BMI, body mass index; CKD, chronic kidney disease; ESKD, end-stage kidney disease; KTx, kidney transplant; PSG, polysomnography.

no difference in the change in AHI between the two groups over a mean of 19.9 ± 8.9 months (median AHI change [Q1, Q3]: 1.6 [–2.3, 3.7] in KTx versus –1.1 [–11.7, 9.2] in No-KTx; *P* = 0.31). There was a wide heterogeneity in the direction and slope of change in the sleep apnea severity in both the groups (**Figure S1, SDC,** http://links.lww.com/TXD/A208). There was no significant difference in the longitudinal changes in any of the other PSG variables examined, including the type of apnea (central, obstructive, or mixed).

Predictors of Sleep Apnea Severity at Follow-up

KTx status was not associated with sleep apnea severity at the time of second PSG in models adjusted for KTx status, age, sex, and BMI (Figure 2). In multivariable median regression, baseline AHI was the only significant predictor of sleep apnea severity at follow-up (β = 3.6 per 5 units, 95% confidence interval (CI) 2.1, 5.2; *P* < 0.001) after adjusting for KTx status, age, sex, and BMI.

Changes in Patient-reported Outcomes

In unadjusted analyses, patients with KTx reported a significant improvement in FACIT-F (42.7 [8.8] versus 38.1 [9.3]; *P* = 0.02), SF-36 MCS (55.7 [5.8] versus 49.2 [9.5]; *P* < 0.01), and SF-36 PCS (45.5 [10.5] versus 41.9 [10.8]; *P* = 0.03) scores as compared to their pre-KTx levels. These remained significant after adjusting for age, sex, and BMI, indicating an improvement in fatigue and HRQOL after KTx. The adjusted effect size of improvement in fatigue and mental HRQOL were moderate (ES 0.55 and 0.62, respectively), while the effect size for improvement in physical HRQOL was small (0.34) (Figure 3). There

TABLE 2.

Baseline (T1) PSG variables in KTx and No-KTx groups

PSG variable	All patients, N = 77	KTx group, N = 39	No-KTx group, N = 38	*P*
Apnea hypopnea index	8.9 (3.4, 25.9)	6.4 (2.6, 18.8)	15.2 (5.1, 28.1)	0.06
Baseline SA severity				0.21
No-mild SA	45 (58.4%)	26 (66.7%)	19 (50.0%)	
Moderate-severe SA	32 (41.6%)	13 (33.3%)	19 (50.0%)	
Central apnea index	0 (0, 0.02)	0 (0, 0.02)	0 (0, 0.02)	0.96
Obstructive apnea index	0.1 (0.04, 0.3)	0.1 (0.03, 0.3)	0.2 (0.1, 0.4)	0.05
% TST under 90%	1.5 (0.5, 5.1)	2.0 (0.5, 4.0)	0.8 (0.5, 7.6)	0.85
TST (min)	368 (306, 428)	387 (334, 454)	333 (291, 417)	0.04
Sleep latency	13.3 (7.7, 37.0)	11.7 (7.0, 25.3)	19.2 (7.8, 41.0)	0.28
WASO	71.7 (43.3, 135)	58.7 (40.8, 92.7)	98.7 (51.8, 156)	0.05
Stage N1 sleep, %TST	10.1 (7.0, 16.6)	11.5 (6.8, 16.2)	8.8 (7.1, 16.9)	0.84
Stage N2 sleep, %TST	58.3 (51.9, 64.6)	56.8 (49.4, 62.8)	60.2 (54.4, 70.1)	0.09
Slow wave sleep, %TST	6.4 (2.1, 14.6)	8.6 (3.9, 16.5)	5.1 (1.1, 7.6)	0.01
Rapid eye movement, %TST	19.8 (15.1, 26.7)	20.7 (16.2, 26.6)	19.7 (13.9, 26.7)	0.73
Periodic leg movement index	34.2 (15.8, 61.4)	30.6 (13.8, 54.5)	34.4 (22.6, 63.0)	0.26

Table shows mean (SD) or median (quartile 1, quartile 3) or frequency (%). *P*-values were based on two-sample *t*-test or Wilcoxon rank sum test for continuous variables and χ^2 or Fisher exact test for categorical variables.
KTx, kidney transplant; PSG, polysomnography; TST, total sleep time; WASO, wakefulness after sleep onset.

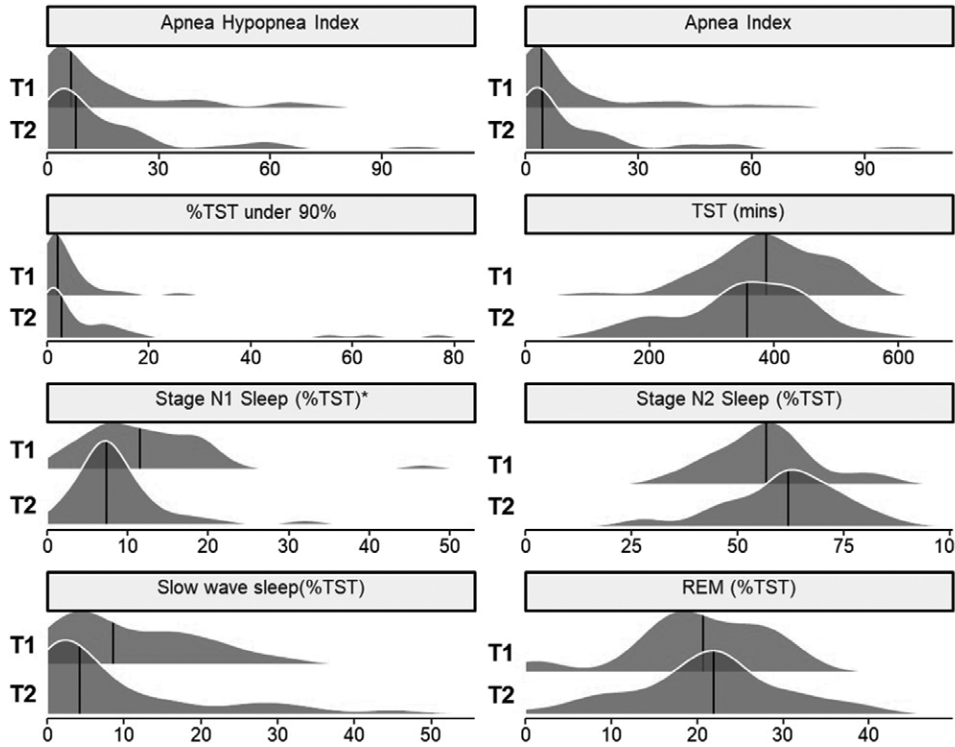

FIGURE 1. Changes in polysomnography variables before (T1) and after (T2) kidney transplant. *Statistically significant ($P < 0.05$) based on Wilcoxon-signed rank test. **Vertical lines in the density curves represent the median.

was no improvement in subjective measures of sleep including ESS, PSQI, or proportion of patients with restless leg syndrome (**Figure S2, SDC,** http://links.lww.com/TXD/A208). In the No-KTx group, there was no significant longitudinal change in any of the patient-reported outcome scores (data not shown).

Meta-analysis of Effect of Kidney Transplantation on Sleep Apnea Severity

To address the limitation of small sample size and power in our study, we conducted a meta-analysis using data from 3 prior studies. Based on a random effects meta-analytic model, the estimated average effect of KTx across studies was small and the lower limit of the 95% CI did not even reach a 5-point reduction in AHI (estimate [95% CI]: −1.4 [−4.4, 1.5]; Figure 4). This suggests that the effect of KTx may be small at best and not clinically meaningful. The pooled estimate from a fixed-effects model was similar (estimate [95% CI]: −1.7 [−3.6, 0.3]).

DISCUSSION

At baseline, 2/3 of the CKD/ESKD patients had SA and the prevalence remained high at 56% even after KTx. Similarly

TABLE 3.

Comparison of magnitude of changes in PSGs from baseline (T1) to follow-up (T2) in KTx and No-KTx groups

Difference in variable	KTx group, N = 39	No-KTx group, N = 38	*P*
Apnea hypopnea index	1.6 (–2.3, 3.7)	–1.1 (–11.7, 9.2)	0.31
Central apnea index	0 (–0.01, 0)	0 (–0.01, 0)	0.95
Obstructive apnea index	0 (–0.1, 0.1)	–0.03 (–0.2, 0.1)	0.35
% TST under 90%	0.7 (–0.8, 6.4)	0.3 (–1.2, 2.4)	0.32
TST	–21 (–84.8, 58)	12.2 (–57.8, 73.7)	0.29
Sleep latency	4.3 (–8.2, 11.3)	–3.7 (–20, 7.8)	0.22
WASO	12.3 (–15.2, 35.7)	10.2 (–38.9, 77.6)	0.84
Stage N1 sleep, %TST	–3.4 (6.5)	-4.6 (10.5)	0.58
Stage N2 sleep, %TST	4.6 (15.1)	4.9 (14.3)	0.92
Slow wave sleep, %TST	–2.1 (10.6)	0.9 (7.2)	0.15
Rapid eye movement, %TST	1 (11.5)	–1.3 (10.1)	0.37
Periodic leg movement index	8.1 (62.2)	–1.2 (42.2)	0.45

Table shows mean (SD) or median (quartile 1, quartile 3). *P*-values were based on two-sample *t*-test or Wilcoxon rank sum test for the differences in change scores from T1 to T2.
KTx, kidney transplant; TST, total sleep time; WASO, wakefulness after sleep onset.

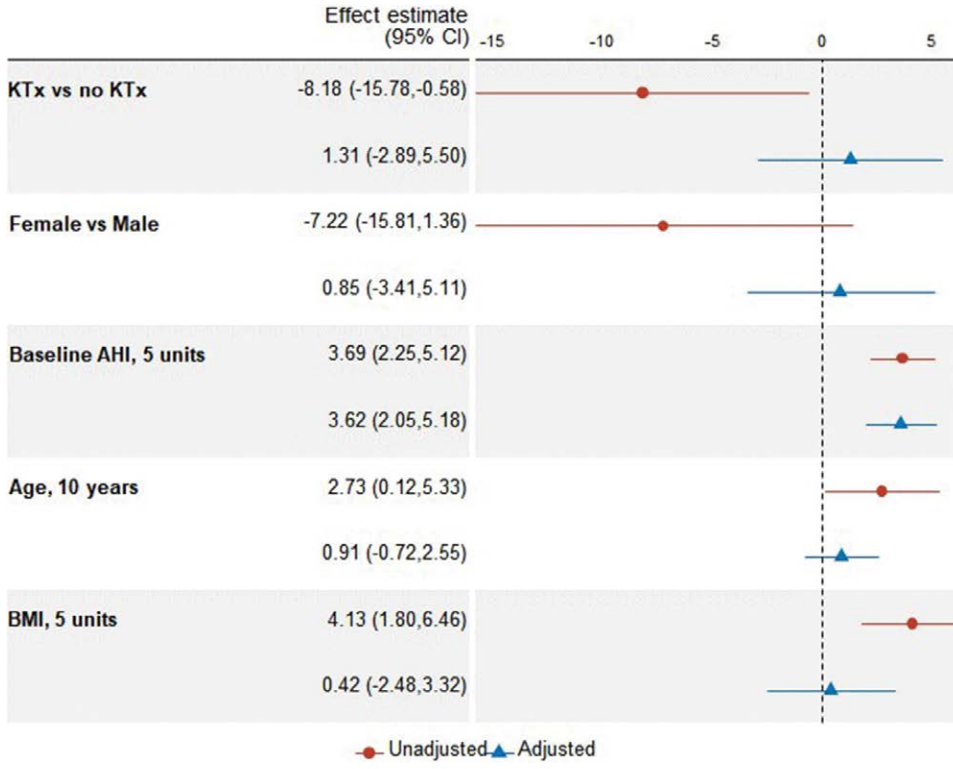

FIGURE 2. Unadjusted and adjusted median regression analyses of T2 apnea-hypopnea index (AHI). *Effect represents median differences in T2 AHI estimated using univariate and multivariable median regression models.

the prevalence of moderate-severe sleep apnea was comparable—44% in the CKD/ESKD patients at baseline and 39% after KTx. Our study did not find an improvement in sleep apnea severity among patients with advanced CKD/ESKD after KTx compared to a group that did not receive a KTx. In adjusted analysis, KTx status was not associated with sleep apnea severity posttransplant. There were clinically meaningful small-moderate improvements in subjective fatigue and HRQOL after KTx.

The high prevalence of SDB in KTx in our study is consistent with previous reports. Molnar et al identified 27% prevalence of patients at high risk of OSA, based on a battery of self-administered questionnaires administered to 841 transplant recipients.[31] In contrast, a case series of 47 KTx patients reported 30% of nonobese and 67% of obese patients having severe SDB (AHI ≥ 30) using objective measurement.[32] However, a study in 163 KTx patients demonstrated lower prevalence of SDB (22%) by PSG, and only 5% were found to have moderate-severe SDB.[32] The reason for much higher prevalence of SDB especially moderate-severe SDB in our study may be due to higher BMI, higher proportion of diabetics, racial differences (18% non-Whites), and perhaps slightly worse renal function post-KTx (Cr 1.7 in our cohort versus ~1.5 mg/dL prior studies).

In advanced CKD/ESKD patients, OSA is felt to be secondary to a combined effect of uremic toxins on upper airway muscle tone and nocturnal rostral fluid shift causing dynamic airway obstruction from varying degrees of fluid

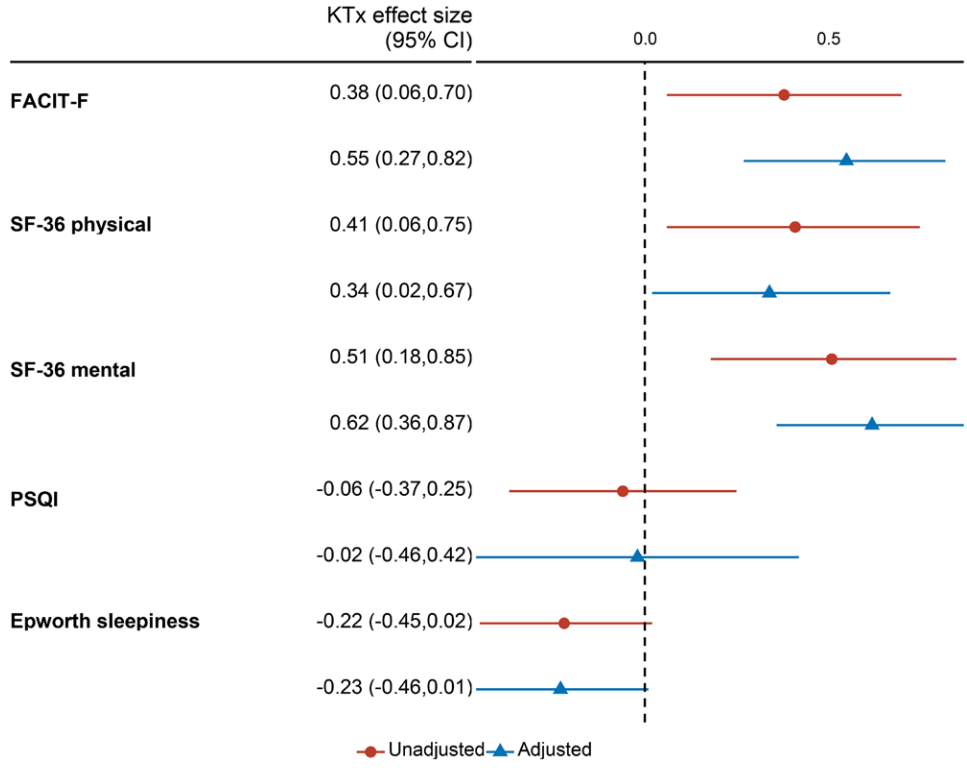

FIGURE 3. Effect size of kidney transplantation on patient-reported outcomes. *Kidney transplant (KTx) effect size represents standardized mean differences. These were estimated from univariate and multivariable linear regression models for the changes in each patient-reported outcome before and after KTx. Multivariable models adjusted for baseline value, gender, age, and body mass index (BMI).

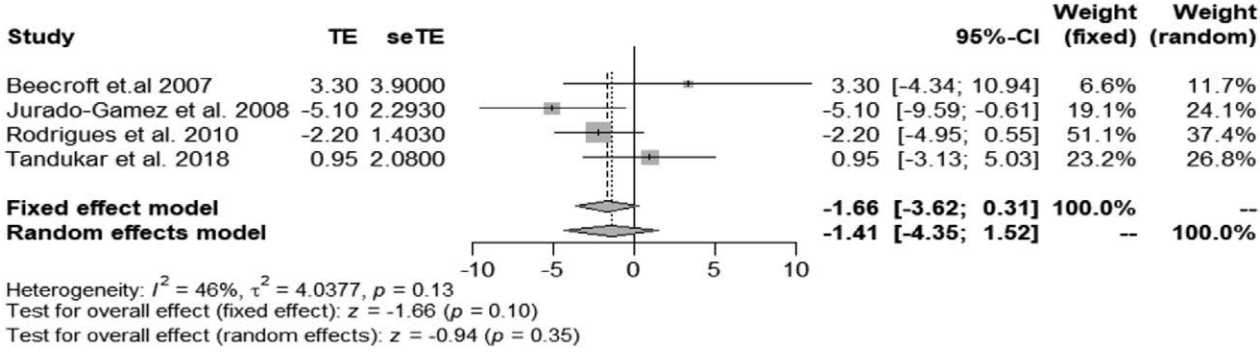

FIGURE 4. Meta-analysis of effect of kidney transplant on sleep apnea severity. seTE, standard error of treatment effect; TE, treatment effect.

overload.[2,10,31,33] Additionally, heightened ventilatory sensitivity to hypercapnia ("loop gain") and compensatory hyperventilation due to vagal response secondary to pulmonary vascular congestion is thought to trigger Cheyne-Stokes respiration-CSA in fluid-overloaded patients.[11] We had hypothesized that the improvement in uremia and fluid overload would improve SDB in KTx patients. Prior studies have shown either an improvement or deterioration of SDB after KTx. Langevin et al reported 2 cases of KTx recipients (one with OSA and the other with CSA), who were cured of sleep apnea after successful transplantation.[2] A longitudinal study in 9 hemodialysis patients showed significant improvement in sleep apnea severity measured by PSG after about 5 months post-KTx. However, this study excluded patients with body weight changes >10% after KTx.[14,15] On the contrary, similar to our study, 2 longitudinal studies—1 with 34 patients and 1 with 18 patients—failed to show improvement in AHI using PSG after KTx.[16] A possible explanation may be an increase in BMI post-KTx perhaps due to improvement in appetite with resolution of uremia or due to use of immunosuppressive regimens, which may include corticosteroids.

Fatigue is a ubiquitous symptom in patients with advanced CKD and ESKD patients on RRT and associated with poor HRQOL.[12] We found FACIT-F score improved by 5 points after KTx, and 3 points are considered clinically minimal important difference.[34] We observed a moderate effect size with clinically meaningful improvement in fatigue and mental HRQOL (SF-36 MCS score improved by 7) and small improvement in physical HRQOL (SF-36 PCS score improved by 4) after KTx. These improvements could be attributed to resolution of uremic symptoms or improvement in dialysis-related fatigue. Our study confirms the improvement in quality of life with KTx seen in prior studies[35,36] and is the first to longitudinally assess changes in fatigue after transplant.

The improvement in fatigue despite no change in subjective or objective sleep in our study supports the multifactorial etiology of fatigue in patients with advanced CKD and ESKD.[5,12,25,37]

Our study has a number of strengths. First, it incorporates the longitudinal comparison of sleep parameters in KTx and No-KTx groups over a period of time. Second, the predominant method of capturing SDB patients in most of the prior studies were subjective measures,[31] pulse oximetry,[38] or wrist actigraphy,[39] with only a small number of studies using PSG[12,38] for diagnosis and assessment of severity. We used both subjective and objective measures in our study population at 2 separate time points for comparison. Third, we were able to account for a number of confounding variables that may impact sleep and fatigue in these patients such as laboratory parameters, BMI, day of PSG (dialysis versus nondialysis day), renal function post-KTx, and medications. Lastly, there was adequate time between the 2 PSGs, and between the KTx and second PSG that allowed us to assess the effect of changes in parameters that are expected to change over time in KTx patients such as the BMI and immunosuppression regimen.

Some limitations must be taken into account while interpreting the results of our study. First, we used unattended, in-home PSG for diagnosing and stratifying sleep disorders by severity. Although full PSG is recommended for diagnosing sleep disorders, in-home PSG has been shown to have findings consistent with the former.[37] Second, 35% of the patients who completed first PSG did not have a follow-up PSG and were not included in this analysis, which may have resulted in selection bias. Third, we were unable to ascertain whether the changes in BMI were a consequence of differences in fluid balance or actual weight gain or loss from improved or worsened nutritional status, respectively. Lastly, although our study has the largest sample size to date, we still lack power to detect a clinically meaningful reduction in AHI. Although we conducted a meta-analysis in an attempt to address this, it had several limitations. First, the studies were heterogeneous with baseline AHI that ranged from 5 to 20 and changes in AHI that ranged from −5.1 to 0.95. The estimated variation across all 4 studies were moderate (I^2 = 46%). Thus, a true single KTx effect may not exist across these studies, rendering fixed-effects analyses invalid. Second, we only have 4 studies with a total patient pool of N = 93, providing imprecise estimates of the effect in both a fixed-effects and random-effects analyses. Third, the SD of the AHI change was needed to conduct the meta-analyses but it was not reported by the other 3 studies. Thus, we had to approximate it based on what we observed in our dataset. Future studies with larger sample sizes are needed to evaluate changes in sleep disorders and fatigue after KTx.

CONCLUSION

More than half KTx recipients had sleep apnea, with 39% having moderate-severe sleep apnea. There was no significant change in sleep apnea severity with KTx. Clinically meaningful, moderate size improvements in patient-reported fatigue and mental HRQOL may be seen with KTx. The significant burden of sleep disorders and fatigue in non-RRT dependent advanced CKD, ESKD, and KTx patients requires urgent attention and further examination.

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