



# Kidney transplantation: a possible solution to obstructive sleep apnea in patients with end-stage kidney disease

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## Abstract

**Introduction** Obstructive sleep apnea (OSA) is frequently reported among patients with chronic kidney disease resulting in considerable morbidity and mortality. OSA may cause repetitive stimulation of the sympathetic nervous system and elevations in pulmonary artery pressure leading to an elevated risk of cardiac and vascular complications in patients with chronic kidney disease. Furthermore, OSA is associated with progressive worsening of kidney injury and loss of renal function.

**Methods** In this systematic review and meta-analysis, we evaluated the effect of renal transplantation on the progression of OSA in patients with end-stage kidney disease.

**Results** The meta-analysis included eight studies with a total of 401 patients. Findings showed that kidney transplantation does not lead to a statistically significant effect on the apnea–hypopnea index (MD 2.6 events/hr, 95% CI –3.2 to 8.3,  $p = 0.21$ ), total sleep time (MD 14.7 min/night, 95% CI –8.4 to 37.8,  $p = 0.76$ ), sleep efficiency (MD 2.5%, 95% CI –1.4 to 6.3,  $p = 0.57$ ), slow wave sleep (MD 0.4% of total sleep time, 95% CI –7.5 to 8.4,  $p = 0.05$ ), and rapid eye movement sleep (MD 0.6% of total sleep time, 95% CI –2.2 to 3.3,  $p = 0.98$ ). There was no statistically significant effect of kidney transplantation on OSA in patients with chronic renal disease.

**Keywords** Kidney transplantation · Sleep apnea · Apnea hypopnea index · End-stage kidney disease

## Introduction

The prevalence of chronic kidney disease (CKD), defined by an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m<sup>2</sup> or the presence of at least one marker of kidney injury including albuminuria, has been on the rise over the last decades, affecting approximately 500 million adults globally [1, 2]. In addition to its strong association with multiple comorbidities including atherosclerosis, hypertension, cerebrovascular disease, dyslipidemia, peripheral vascular disease, and cardiovascular disease and myocardial infarction, CKD is also strongly associated with obstructive sleep apnea (OSA) [3–6]. The repetitive activation of the sympathetic nervous system and the development of pulmonary artery hypertension which are both common consequences of OSA further elevate the risk of cardiac and vascular complications in patients with CKD [7, 8]. Even though the exact pathophysiological mechanism underlying the elevated risk of OSA in patients with CKD remains controversial, multiple hypotheses including volume overload, compensatory respiratory alkalosis in response to metabolic acidosis and/

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or uremic toxins have been postulated [8, 9]. In addition, multiple studies have shown an association between OSA-induced nocturnal hypoxemia and kidney injury as well as loss of renal function [10, 11]. Furthermore, central sleep apnea, a potential complication that may mimic OSA and may not always be distinguishable, is common in patients with CKD, especially in individuals receiving renal replacement therapy or those with comorbid congestive heart failure [12, 13]. Our meta-analysis aimed to evaluate the effect of kidney transplantation in the reversal of OSA and its associated complications in patients with end-stage kidney disease (ESKD).

## Materials and methods

Guidelines of the Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology [14], Quality of Reporting of Meta-Analyses [15], and the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines [16] have been followed in this meta-analysis.

### Literature search

Cochrane Central Register of Controlled Trials (Wiley), Embase (Elsevier), and PubMed/Medline Web of Science databases were used for the literature search in June 2022 with the following keywords and their variations or combinations: “end stage renal disease,” “ESRD,” “ESKD,” “end stage kidney disease,” “hemodialysis,” “chronic kidney disease,” “CKD,” “peritoneal dialysis,” “dialysis,” “renal replacement therapy,” “sleep apnea,” “apnea,” “hypopnea,” “apnea–hypopnea index,” “obstructive sleep apnea,” “kidney transplantation,” “sleep disorder,” “renal transplantation,” and “transplantation.” All the authors have taken part in the assessment of the titles and abstracts the studies independently, and a consensus was achieved after examining and discussing each study in detail. The references were evaluated to not omit any additional study. The full-text evaluation of the studies that remained were performed by the authors after preliminarily eliminating from the titles and abstracts. Furthermore, the chosen studies were assessed according to the inclusion and exclusion criteria of this meta-analysis study which were as follows: any original article (i.e., randomized control trials, prospective cohort, case control, retrospective cohort, and cross-over study) that investigates kidney transplantation on the incidence or prevalence or severity of sleep apnea which is in a peer-reviewed journal in English before June 2022. Studies not including baseline data regarding sleep apnea prior to kidney transplantation or other types of study designs (i.e., case reports, case series, editorials, commentaries review, systematic review and meta-analysis), studies with unpublished data, or inadequate

description of the outcomes and missing data were excluded from this meta-analysis study. Figure 1 is summarized the study selection process.

### Quality assessment

The Newcastle–Ottawa Scale was used for evaluating the quality of the studies. The Newcastle–Ottawa Scale consists of three main parts: the selection of study groups, comparability of the groups, and assessment of outcomes with the highest quality of research given nine stars. The quality assessment was conducted with the participation of all authors, and a consensus decision was reached for each study.

### Statistical analysis

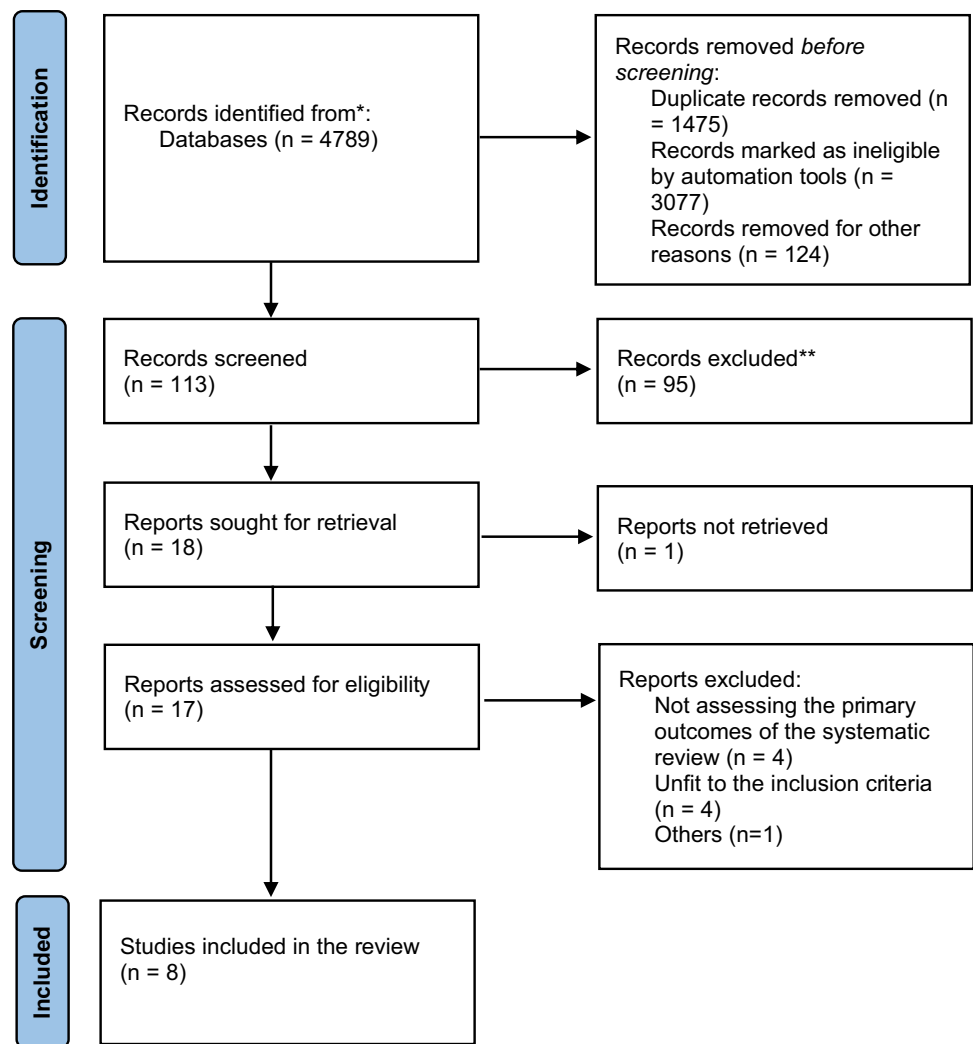
Review Manager (RevMan) Version 5.4 (The Cochrane Collaboration 2012) was used for statistical analyses [17]. For the continuous outcomes, random-effects model for meta-analysis was used and reported all the values as mean and standard deviation (AHI (events/hr), total sleep time (TST) (min/night), sleep efficiency (%), slow wave sleep (% TST), rapid eye movement (REM) sleep (% TST), and BMI (kg/m<sup>2</sup>)). When the mean difference and standard deviation were reported for separated groups, we calculated the group’s mean difference and standard deviation by using the RevMan calculator. Standard formulas were used to transform median and interquartile range to mean and standard deviation, if needed [18]. The inconsistencies throughout the individual studies were evaluated via the  $I^2$  statistic [19]. An  $I^2 > 50\%$  indicated a large heterogeneity which was not explained by chance.  $P$  value  $< 0.05$  was defined as statistically significant.

## Results

Our analysis included eight prospective, cohort studies on kidney transplant recipients (Table 1) [5, 20–26]. A total of 401 patients were included in the meta-analysis (with a minimum of 9 [5] and a maximum of 221 [23]).

Studies evaluated the effect of kidney transplantation on sleep quality by assessing different parameters either measured through polysomnography (PSG) or reported through standardized questionnaires such as the Epworth Sleepiness Scale (ESS). For this analysis, we selected the following parameters: apnea–hypopnea index (AHI in events/hr), TST (min/night), sleep efficiency (%), slow wave sleep (%TST), and REM sleep (%TST). Additionally, an analysis of the BMI, before and after transplantation was performed.

An analysis of the time trend of nocturnal O<sub>2</sub> saturation could not be performed, since these data were reported

**Fig. 1** PRISMA flow chart of the study selection process

differently throughout the studies: oxygen desaturation index (ODI) in Mallamaci 2020, Rodrigues 2010, and Ognà 2019; minimal  $O_2$  saturation in Mallamaci 2020 and Jurado-Gamez 2008, % TST under 90% in Tandukar 2019 and Jurado-Gamez 2008; and mean  $O_2$  saturation in Beecroft 2007 and Mahajan 2017.

### Apnea–hypopnea index (AHI, events/hr)

All eight studies [5, 20–26] reported AHI [27] as the primary indicator for sleep apnea (Fig. 2). AHI was measured through polysomnography (PSG) in all cohorts before and after transplantation. Differences in the final results did not reach statistical significance. Two of the studies [20, 21] divided their cohorts into two groups, specifically apneic and non-apneic groups according to an  $AHI > 10/h$  in pre-transplant PSG. Another study [26] selected its cohort from adult patients with ESKD who were on the kidney transplantation waiting list and were screened by pre-transplant PSG, only apneic patients with severe pre-transplantation sleep

apnea ( $AHI \geq 15/h$ ) who underwent kidney transplantations were reassessed after 6 months (post-transplant) using the same protocol. Thus, we chose to conduct a sub-analysis on the evolution of AHI in these groups (Fig. 3). The result did not reach statistical significance (MD 2.6 events/hr, 95% CI – 3.2–8.3,  $P = 0.21$ ).

### Total sleep time (TST, min/night)

Three studies [20, 22, 26] reported the total sleep time, before and after transplantation (Fig. 4). Differences for these results did not reach statistical significance (MD 14.7 min/night, 95% CI – 8.4–37.8,  $P = 0.76$ ). There was no heterogeneity in this cohort ( $I^2 = 0\%$ ).

### Sleep efficiency (%)

Sleep efficiency was reported as an outcome in five studies [5, 20, 22, 24, 26] (Fig. 5). Four studies reported an increase

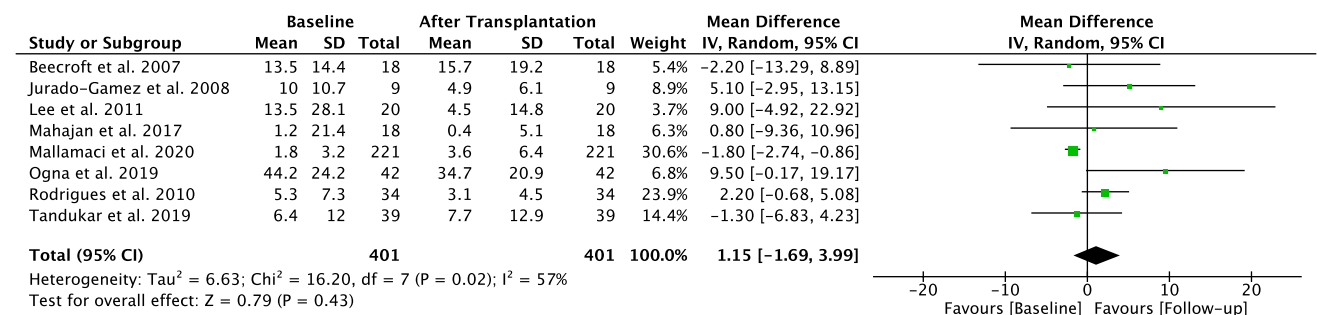
**Table 1** General characteristics of the included studies evaluating the effect of renal transplantation in patients with sleep-disordered breathing

Study	Study design	Characteristics of the participants	The Newcastle–Ottawa score of the Study
Jurado-Gómez et al. 2008 [5]	Prospective cohort study	Transplant group ( $N=9$ ) Mean age: 42 (SD: 16) Gender: 7 (77.8%) male	Total score = 7 ● Selection: 3 ● Comparability: 2 ● Outcome: 2
Beecroft et al. 2007 [20]	Prospective cohort study	Non-apneic group ( $N=7$ ) Mean age: 42 (SD: 9) Gender: 3 (42.9%) male Treatment at baseline: Hemodialysis: 3 (42.9%) Peritoneal dialysis: 0 (0%) Pre-dialysis: 4 (57.1%) Apneic group ( $N=11$ ) Mean age: 47 (SD: 13) Gender: 8 (72.7%) male Treatment at baseline: Hemodialysis: 8 (72.7%) Peritoneal dialysis: 1 (9.0%) Pre-dialysis: 2 (18.2%)	Total score = 8 ● Selection: 3 ● Comparability: 2 ● Outcome: 3
Lee et al. 2011 [21]	Prospective cohort study	Non-apneic group ( $N=8$ ) Median age: 40 (range: 25, 60) Gender: 50% male Body mass index ( $\text{kg}/\text{m}^2$ ): 24.0 (range: 17.8, 26.6) Treatment at baseline: Hemodialysis: 5 (62.5%) Peritoneal dialysis: 1 (12.5%) Pre-dialysis: 2 (25%) Dialysis duration (months): 14 (range: 0, 215) Apneic group ( $N=12$ ) Median age: 41 (range: 23, 59) Gender: 75% male Body mass index ( $\text{kg}/\text{m}^2$ ): 21.0 (range: 17.0, 32.5) Treatment at baseline: Hemodialysis: 8 (66.7%) Peritoneal dialysis: 2 (16.7%) Pre-dialysis: 2 (16.7%) Dialysis duration (months): 11 (range: 0, 102)	Total score = 7 ● Selection: 3 ● Comparability: 2 ● Outcome: 1
Mahajan et al. 2018 [22]	Prospective cohort study	Transplant group ( $N=18$ ) Mean age: 28.9 (SD: 8.9) Gender: 14 (77.8%) male	Total score = 7 ● Selection: 3 ● Comparability: 2 ● Outcome: 2
Mallamaci et al. 2020 [23]	Prospective cohort study	Transplant group ( $N=221$ ) Mean age: 46.9 (SD: 11.6) Gender: 70.1% male Background cardiovascular complications (%): 10.9% Diabetes (%): 9%	Total score = 6 ● Selection: 3 ● Comparability: 1 ● Outcome: 2
Rodrigues et al. 2010 [24]	Prospective cohort study	Transplant group ( $N=34$ ) Mean age: 35 (SD: 10.4) Gender: 58% male	Total score = 6 ● Selection: 3 ● Comparability: 1 ● Outcome: 2

**Table 1** (continued)

Study	Study design	Characteristics of the participants	The Newcastle–Ottawa score of the Study
Tandukar et al. 2019 [25]	Prospective cohort study	Control group (N=38) Mean age: 53.4 Gender: 23 (60.5%) male Cardiovascular disease: 9 (24.3%) Diabetes: 20 (54.1%) Stroke: 3 (8.1%) Hypertension: 30 (88.2%) Transplant group (N=39) Mean age: 48 Gender: 28 (71.8%) male Cardiovascular disease: 4 (10.3%) Diabetes: 10 (25.6%) Stroke: 1 (2.6%) Hypertension: 36 (92.3%)	Total score = 7 ● Selection: 3 ● Comparability: 2 ● Outcome: 2
Ogna et al. 2019 [26]	Prospective cohort study	Control group (N=27) Mean age: 56.0 (SD: 8.6) Gender: 22 (81.5%) male Diabetes: 11 (40.7%) Hypertension: 25 (92.6%) Renal replacement therapy: Hemodialysis: 12 (46.2%) Peritoneal dialysis: 6 (23.1%) ESKD without RRT: 8 (30.7%) Transplant group (N=42) Mean age: 56.6 (SD: 9.7) Gender: 33 (78.6%) male Diabetes: 12 (28.6%) Hypertension: 38 (90.5%) Renal replacement therapy: Hemodialysis: 22 (52.4%) Peritoneal dialysis: 9 (21.4%) ESKD without RRT: 11 (26.2%)	Total score = 7 ● Selection: 3 ● Comparability: 2 ● Outcome: 2

ESKD end-stage kidney disease, RRT renal replacement therapy



**Fig. 2** Forest plot of the included studies for apnea-hypopnea index

in sleep efficiency, with only one study reporting a negative effect of kidney transplantation [22]. Overall, differences in the results did not reach statistical significance (MD 2.5%, 95% CI -1.4–6.3, P=0.57).

**Slow wave sleep (% TST)**

Three studies [20, 22, 24] reported the time of slow wave sleep, reported to the total sleep time (stages 3 and 4 of the non-REM sleep) (Fig. 6). This analysis showed that kidney transplantation did not influence this parameter (MD 0.4% total sleep time, CI 95% -7.5–8.4, P=0.05).

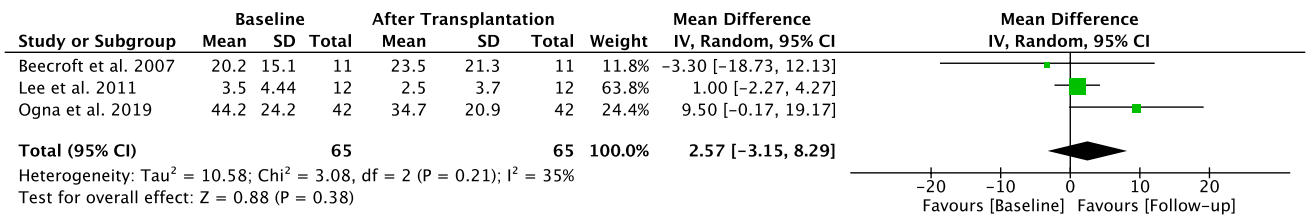


Fig. 3 Forest plot of the included studies for sub-analysis on apnea–hypopnea index

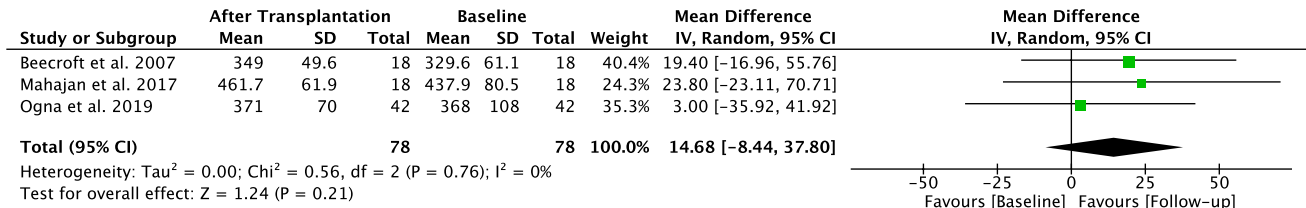


Fig. 4 Forest plot of the included studies for total sleep time

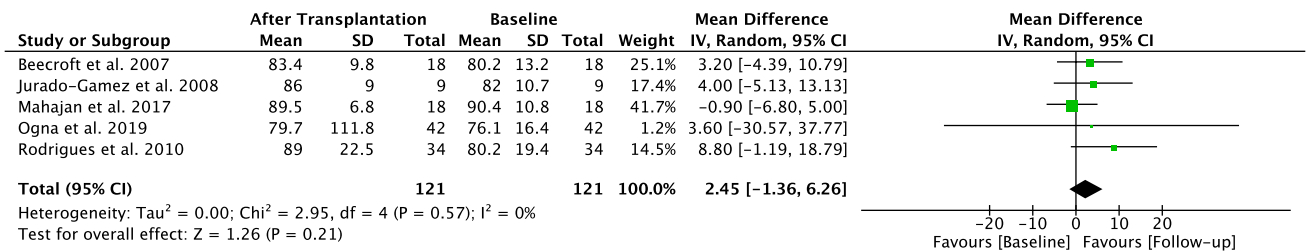


Fig. 5 Forest plot of the included studies for sleep efficiency (%)

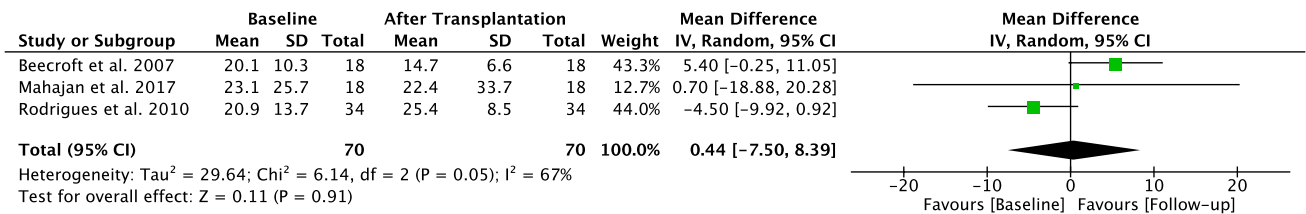


Fig. 6 Forest plot of the included studies for slow wave sleep (%total sleep time)

### Rapid eye movement sleep (REM, % TST)

Four studies [5, 20, 22, 24] analyzed the five stages of sleep (non-REM, stages 1 to 4, and REM) separately through polysomnography (Fig. 7). While these studies reported an overall increase in total sleep time, there were no significant reports on the increase or decrease of the duration of the different sleep stages after kidney transplantation (MD 0.6% TST, 95% CI -2.2–3.3, P=0.98).

### Body mass index (BMI, kg/m<sup>2</sup>)

Five studies [20, 22, 24–26] reported the BMI at baseline and post kidney transplantation (Fig. 8). All reported an

increase in BMI after transplantation, confirmed by the overall analysis (MD 1.2 kg/m<sup>2</sup>, 95% CI 0.2–2.1, P=0.69). Heterogeneity was absent in this cohort, with an I<sup>2</sup> of 0%.

## Discussion

In this meta-analysis which includes eight studies with a total of 401 participants, the effect of kidney transplantation on the progression of sleep apnea in patients with ESKD was assessed. The meta-analysis showed that kidney transplantation does not lead to a statistically significant effect in apnea–hypopnea index, total sleep time, sleep efficiency,

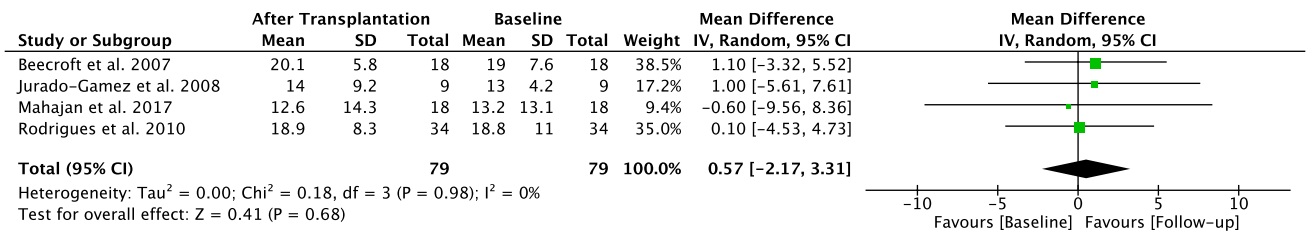


Fig. 7 Forest plot of the included studies for REM sleep (%total sleep time)

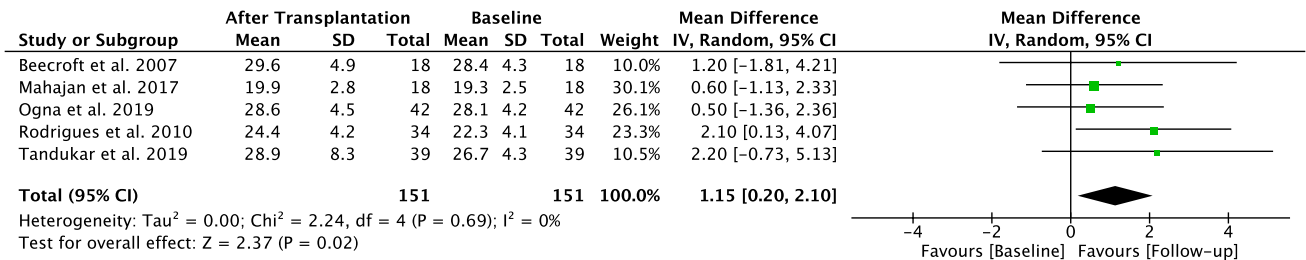


Fig. 8 Forest plot of the included studies for body mass index

slow wave sleep, or REM sleep. It is crucial to emphasize the considerable variation across individual studies. The meta-analysis is the first study evaluating the effect of kidney transplantation on sleep apnea, a highly common comorbidity and cause of morbidity in patients with ESKD.

The associations between ESKD and sleep apnea including its potential underlying pathophysiological mechanism have largely been investigated in multiple pre-clinical and clinical studies without a definitive result. In addition to the traditional risk factors of OSA in the general population including metabolic syndrome, obesity, and anatomical variations of airways, individuals with ESKD are prone to develop obstructive or central sleep apnea as a result of fluid overload. Studies demonstrating the association between internal jugular vein dilatation and sleep apnea in patients with ESKD and attenuation of such findings following nocturnal dialysis support the pathophysiological role of fluid overload in sleep apnea [28, 29]. Similarly, nocturnal rostral fluid shifts and fluid overload were also suggested to contribute to the high risk of sleep apnea in patients with heart failure [29]. In a cross-sectional study conducted on 100 individuals with CKD who were not on renal replacement therapy, fluid overload markers such as serum brain natriuretic peptide levels and the diameter of inferior vena cava were shown to correlate with sleep apnea, independent from the traditional confounding factors [30]. Similar findings have been established in few other clinical studies [27, 31]. Fluid overload may lead to the stimulation of pulmonary irritant receptors causing cycles of hyperventilation and apnea [32]. In addition, the respiratory adaptation to metabolic acidosis and uremia, which are the complications of

ESKD, alters chemoreceptor sensitivity and enhances central and peripheral chemoreflexes. These augmented reflexes may impair the stability of ventilation and may predispose to sleep apnea [4, 33]. Obstructive sleep apnea may develop due to neuropathy or myopathy secondary to the complications associated with ESKD such as chronic uremia, which can disrupt the upper airway muscles, and cause compromised upper airway dynamics [4, 33]. Furthermore, the association between sleep apnea and renal function rather appears to be bidirectional. Patients with nocturnal hypoxia have higher risk of renal function decline after controlling for confounders such as diabetes, BMI, age, and heart failure according to a prospective study conducted on 858 patients with a 2 year follow-up period [10]. Another study conducted on 161 patients with stage 3–4 CKD demonstrated that patients with 4% oxygen desaturation index over 15% developed three to four times higher decline in eGFR over a 12-month follow-up period [11].

The current meta-analysis study is significant by being the first meta-analysis investigating the effects of kidney transplantation on sleep parameters in patients with ESKD. However, we appreciate certain limitations to our results. First, the number of total participants is considerably low, with more than half of the participants from single clinical study which affects the generalizability of our results. Second, there was a statistically significant increase in BMI which is a known strong risk factor for sleep apnea. Therefore, the increased BMI in renal transplant patients may undermine the improvements gained from the transplantation procedure and may have prevented the investigated parameters from reaching statistical significance. Furthermore,

one reason for AHI to remain similar to baseline despite a higher BMI after kidney transplantation could be the better management of fluid overload. Another explanation could be that the higher BMI might potentially be a result of an increase in muscle mass and not due to fat deposits following renal transplantation, thus, not leading to a change in sleep parameters [34, 35]. Third, considerable variations exist across individual studies regarding the investigated parameters, study design, and patient characteristics all of which limit the evaluation of results. Fourth, potential confounding factors including BMI, anatomical variations, comorbid medical conditions including heart failure and hypertension have not been adequately eliminated or assessed in subgroup analysis of most included studies.

The effects of renal transplantation in improving OSA in patients with ESKD did not reach statistically significant differences.

**Author contribution** Mehmet Kanbay, Sidar Copur, Carina Ureche, and Alexandra Covic contributed substantially to the conception or design of the work. Carina Ureche, Alexandra Covic, and Mehmet Kanbay contributed substantially to acquisition, analysis, or interpretation of data. Mehmet Kanbay, Sidar Copur, Carina Ureche, Bugra H. Esen, and Cem Tanriover drafted the manuscript. Mehmet Kanbay, Adrian Covic, Carina Ureche, Alexandra Covic, Cem Tanriover, Asiye Kanbay, and Sidar Copur were involved in the revision of the manuscript for important intellectual content.

**Data availability** This is not applicable.

## Declarations

**Ethical approval** This is not applicable.

**Conflict of interest** The authors declare no competing interests.

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