Original article

Title: Depressive symptoms are associated with objectively measured sleep parameters in kidney transplant recipients

Subtitle: Depression, sleep and kidney transplantation

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Abstract:

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Introduction: Both depression and sleep complaints are very prevalent among kidney transplant (kTx) recipients. However, details of the complex relationship between sleep and depression in this population are not well documented. Thus we investigated the association between depressive symptoms and sleep macrostructure parameters among prevalent kTx recipients.

Methods: 95 kTx recipients participated in the study (54 males, mean age 51±13 years, BMI 26±4 kg/m^2, estimated glomerular filtration rate 53±19 ml/min/1.73m^2). Symptoms of depression were assessed by the Center for Epidemiologic Studies - Depression Scale (CES-D). After one-night polysomnography each recording was visually scored and sleep macrostructure was analysed.

Results: The CES-D score was significantly associated with the amount of stage 2 sleep ($r=0.20$, $p<0.05$), REM latency ($r=0.21$, $p<0.05$) and REM percentage ($r=-0.24$, $p<0.05$), but not with the amount of slow wave sleep ($r=-0.12$, $p>0.05$). In multivariable linear regression models the CES-D score was independently associated with the amount of stage 2 sleep (β: 0.205; CI: 0.001-0.409; $p=0.05$) and REM latency (β: 0.234; CI: 0.001-0.468; $p=0.05$) after adjustment for potential confounders.

Conclusion: Depressive symptoms among kTx recipients are associated with increased amount of stage 2 sleep and prolonged REM latency. Further studies are needed to confirm our findings and understand potential clinical implications.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Depression and sleep problems are very prevalent in kidney transplant recipients. However, the association between sleep structure and subjective depressive symptoms has not been investigated in this population.

Study Impact: We demonstrate, for the first time, a connection between depressive symptoms and objectively assessed sleep macrostructure among kidney transplant recipients. These results represent an important step in the understanding of the underlying processes linking depression and sleep among these patients.

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Introduction

Depression is one of the most prevalent mental health conditions in patients with chronic kidney disease (CKD);[1-4] furthermore it is an important determinant of impaired quality of life[5,6]. Among kidney transplant (kTx) recipients depression is associated with reduced adherence and also with increased morbidity, graft loss and mortality[7-13]. Poor sleep and various sleep problems are also frequent complaints among kTx recipients[14,15]. Earlier we reported that chronic insomnia was independently associated with the presence of depression in kTx recipients[16].

In the general population there is a strong and bidirectional relationship between depression and sleep[17]. This is also reflected in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) definition of major depression (MD),[18] as sleep complaints are core symptoms of MD. Several objective sleep parameters are different in MD patiens than in healthy controls. Patients with MD have decreased amount of slow wave sleep (SWS) and shortened rapid eye movement (REM) latency with increased amount of REM sleep[19-22].

The exact mechanisms and factors that may link depression to poor clinical outcomes among kTx recipients are not well defined yet. In a recent review focusing on kTx and depression[23] sleep is not at all mentioned. This may be due to the complete lack of polysomnography (PSG) studies that assess the association between sleep and depression in this population. The frequent co-occurance of subjective sleep complaints and depression among kTx recipients[16] suggests that the relationship between the two conditions may be similar to the association described in the general population[24-26]. This highlights the clinical significance of sleep problems among kTx recipients, since they are potentially modifiable and interventions focusing on enhancing sleep may help to improve depressive symptoms[27].

Despite the significance of depression among kTx recipients and its well-known associations with sleep problems in the general population, there is a lack of information regarding the connection of depression and sleep parameters assessed by PSG among kTx recipients. Evaluating sleep structure with PSG and its associations with depressive symptoms is an important step in the understanding of the pathophysiology behind the subjective symptoms. Thus, in this study, we aimed to investigate the macrostructure parameters of sleep and we hypothesized that, similarly to patients with depression, less SWS, shortened REM sleep latency and higher proportion of REM sleep are associated with depressive symptoms in this patient population.

Materials and methods

Sample of patients and data collection

Data for this analysis were obtained from the ‘‘SLeep disorders Evaluation in Patients after kidney Transplantation (SLEPT) study’’[28-34]. Potentially eligible patients were selected from all prevalent adult kTx recipients (‘‘total clinic population’’; n = 1,214) who were regularly followed at a single outpatient academic transplant center, the kidney transplant clinic of the Department of Transplantation and Surgery at the Semmelweis University, Budapest, Hungary (Figure 1). All patients followed at the clinic on December 31, 2006 were considered for enrollment in the Malnutrition and inflammation in transplant (MINIT-HU) study. After applying exclusion criteria (transplant received within less than 3 months, presence of active and acute respiratory disorder, acute infection, or hospitalization within 1 month, surgery within 3 months), 1,198 patients remained (‘‘base population’’). From this ‘‘base population,’’ we randomly selected and approached 150 patients (‘‘kTx study sample’’) using the simple random sampling strategy offered by SPSS 15.0 (IBM Corporation, Armonk, New York, USA). The creation of cohort has been described previously[28-34]. From these 150 eligible patients 100 individuals agreed to participate and they underwent one-night PSG (’’kTx participant sample”). From this sample of 100 patients, 3 were excluded of our analysis because of missing depression score and 2 were excluded because of antidepressant pharmacotherapy. Thus, the final ’’kTx macrostructure sample’’ included 95 patients whose PSG recordings were analysed in this report. Demographic, anamnestic and questionnaire-based data were collected at enrollment, including age, sex, etiology of end-stage kidney disease (ESKD), transplantation-related data, medication use, and assessment of depression and insomnia symptoms.

Assessment of depression

The Hungarian version of the Center for Epidemiologic Studies - Depression (CES-D) scale[35] was prepared according to the recommended procedure[36] and was validated by our team in Hungarian kTx recipients[37]. The CES-D scale consists of 20 items, the score range is 0-60, with higher scores indicating lower mood. Subjects are asked to grade how frequently their complaints occured and how long lasted (rarely, 1-2 days, 3-4 days, 5-7 days) within the last week. In the present analysis the CES-D score was used to describe the severity of depressive symptoms in the sample. In addition, a cut-off score of 18 was used to estimate the frequency of clinically significant depression in patients with CKD as suggested by Hedayati et al.[38].

Polysomnography (PSG) and sleep staging

Standard, attended overnight PSG was performed in acoustically isolated and video-monitored sleep laboratory equipped with four individual suits (SOMNOscreenTM PSG Tele, SOMNOmedics GmBH, Germany, CE0494). The following data were recorded: 5 EEG channels (A1, A2, C3, C4, Cz), electrooculogram, chin electromyography, tibial electromyography, electrocardiography, airflow, thoracic–abdominal movements, pulse oximetry, tracheal sound (snoring), and body position. The ground and common reference electrodes were placed at Fpz and Cz, respectively. EEG signals were sampled and stored at 128 Hz, low- and high-pass filters were set at 35 Hz and 0.2 Hz, respectively. All recordings were performed on weekdays, the timing of "lights off" and "lights on" were uniformly set around 22:00 and 6:00, respectively.

Recordings were manually scored by two somnologists (MZM, ASL). Sleep stages were determined in 30 sec epochs according to Rechtschaffen and Kales[39]. Sleep macrostructure was characterized by the following variables: sleep onset latency (SOL: time elapsed from "lights off " to the first occurrence of sleep stage 2); total sleep time (TST); wake after sleep onset (WASO: time spent awake from sleep onset to "lights on"), sleep efficiency (ratio of total sleep time over the time spent in bed); percentages of stages 1, 2, slow wave sleep (SWS: stages 3 and 4 combined) and percentage and latency of REM sleep. Respiratory events, periodic leg movements and microarousals were scored according to standard criteria[40,41]. Apnea was defined as the absence of airflow for more than 10 sec; hypopnea was defined as a clearly discernible reduction in airflow for more than 10 sec associated with an arousal and/or 3% reduction in oxygen saturation. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. Periodic limb movements were defined as limb movements with duration of 0.5–5 sec; inter-movement interval of 5–90 sec; and separation criteria for limb movements occurring in both legs: more than 5 sec between onsets. The periodic limb movement index (PLMI) was defined as the number of limb movements per hours during sleep.

Assessment of insomnia, restless legs syndrome and comorbidities

The Athens Insomnia Scale (AIS) was used to assess sleep complaints and identify possible cases of insomnia[42,43]. The AIS consists of eight items, score range 0–24, with higher scores indicating worse sleep. Subjects are asked to grade the severity of the sleep complaints (absent, mild, severe, very severe) only if the particular complaint occurred at least three times per week during the last month. A cut-off score of 10 has been suggested for epidemiological studies, providing acceptable sensitivity and specificity to detect clinically significant insomnia[43]. The English version of the AIS had been previously translated and validated by our group[44].

Symptoms of restless legs syndrome (RLS) were identified by using the RLS Questionnaire (RLSQ) completed by the patients. The original version of the RLSQ had been carefully developed to cover the

four diagnostic criteria of RLS and was shown to be a reliable screening instrument[45]. The original instrument was used in an epidemiologic survey[46] and the Hungarian version was used in our earlier studies involving different populations with CKD[47-49].

Comorbidity was assessed by the modified Charlson Comorbidity Index[50] completed by the main responsible transplant physician of the participant. Information about medication use was obtained from the questionnaires and the medical charts.

Laboratory data

Laboratory data were extracted from the medical charts, including blood hemoglobin, serum albumin and creatinine. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease EPIdemiology collaboration) formula[51].

Transplantation and donor related data

Transplantation-related information collected included current medications, transplant and dialysis ''vintage'' (i.e., time elapsed since transplantation or time spent on dialysis prior to transplantation), history of acute rejection, age and sex of donor and history of delayed graft function. Time elapsed since the initiation of the first treatment for ESKD - cumulative ESKD time - was also calculated. Standard maintenance immunosuppressant (IS) therapy generally consisted of prednisolone, either cyclosporine A microemulsion formulation or tacrolimus, combined with mycophenolate mofetil or azathioprine, everolimus or sirolimus.

Ethics approval

The study was approved by the Ethics Board of the Semmelweis University (4/2007). Before enrollment, patients received detailed verbal and written information about the aims and protocol of the study and signed an informed consent.

Statistical analysis

Statistical analysis was carried out using STATA 13.0 software. Continuous variables were compared using Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were analyzed using the chi-square test or the Fisher's exact test if the observation numbers were low. Bivariate analysis was performed using Pearson and Spearman rank correlation analysis.

We analyzed the association between the CES-D score and the selected sleep macrostructure parameters with multivariable linear regression analyses. The models were built with the sleep parameter as the dependent variable and the CES-D score as independent variable. In the models the potential confounders, which were selected based on theoretical considerations, were additionally

subject to backward stepwise selection using a removal condition (p>0.2): AIS score, graft function (eGFR), AHI, PLMI, presence or absence of RLS and hypnotic medication use. Age, sex and CES-D score were included in the models with forced selection. We used square root transformation to achieve normal distribution of the variable where it was necessary (REM latency). In all statistics, two-sided tests were used and $p<0.05$ was considered statistically significant.

Results

Demographic data and baseline characteristics of the sample

Of the 150 eligible patients (‘‘kTx study sample,’’ see „Methods” above), 50 individuals (33%) refused to participate. Consequently, the ‘‘kTx participant sample’’’ who underwent PSG included 100 Tx patients (Figure 1). There were no significant differences regarding age and sex between participants and those who refused to participate (data not shown). The basic characteristics (age, sex, eGFR, serum albumin) of the ‘‘kTx participant sample’’ were similar to the characteristics of the ‘‘total clinic population’’ (data not shown).

Of the 100 patients in the ’’kTx participant sample’’ we excluded 5 patients; 3 patients had missing CES-D score and 2 patients were excluded because of treatment with antidepressant medication. Thus, the final ’’kTx macrostructure sample’’ included 95 patients (Figure 1). The demographic and laboratory parameters, the comorbid conditions and transplantation related data of the ’’kTx macrostructure sample” are presented in Table 1.

Prevalence and severity of depression and associations with demographics

The median of the CES-D score was 10 (IQR: 11) in the sample. One fifth of the patients scored 18 or higher indicating high risk of depressive symptoms[38] (Table 1). High depression risk was associated with high risk of insomnia and RLS, furthermore, these patients were taking significantly more hypnotic medication. Female gender and dialysis vintage were nearly significantly related to high depression risk.

Association between depressive symptoms and sleep quality

High risk for depression was significantly associated with less REM sleep and longer REM latency. Additionally, there was a tendency for more stage 2 sleep (Table 2). The proportion of SWS was not associated with high risk for depression (Table 2). CES-D score, a continuous measure of depression symptom severity, was significantly associated with subjective insomnia complaints as measured by the AIS score, with more stage 2 sleep, longer REM latency and less REM sleep, but not with the proportion of SWS (Table 3).

Multivariable analysis

To assess the independent association between depressive symptoms and sleep macrostructure we utilized multivariable analysis (Table 4). The selected sleep macrostructure parameters (proportion of SWS and REM sleep, REM sleep latency) were included in the multivariable models as dependent variables. Additionally, we also included the proportion of stage 2 sleep as dependent variable based on the results of the univariable analyses. Higher proportion of stage 2 sleep and longer REM latency were significantly associated with depression severity independent of other covariables. However, the association of REM sleep percentage with the CES-D score diminished after controlling for covariables. Similarly, the proportion of SWS was not associated with the CES-D score in the multivariable analysis.

Discussion

As far as we know, this is the first study that assessed the association of depressive symptoms and sleep architecture of kTx recipients. Our main finding is that severity of depressive symptoms is associated with increased proportion of stage 2 sleep and longer REM latency, independently of important covariables. In our dataset depressive symptoms were not associated with decreased SWS among kTx recipients.

There has been a growing interest in detailed assessment of sleep among patients with various stages of CKD[52-54] and there is an increasing focus on patient reported outcomes[55]. However, these earlier studies were performed using in-home PSG and did not particularly focus on kTx recipients. Laboratory assessed PSG studies among the kTx recipient population included much fewer patients (n_1 = 18; n_2 = 9; n_3 = 34, respectively) and mainly focused on sleep apnea and the change of the sleep structure associated with apnea treatment or transplantation[56-58]. Although some sleep macrostructure parameters were reported in these studies, little attention was paid to stage 2 sleep or REM sleep.

We found a significant association of stage 2 sleep with depressive symptoms among kTx recipients. Another study that assessed the sleep architecture of patients with CKD and ESKD reported significant association between increased stage 2 sleep and severe fatigue[52], without the significant involvement of SWS. This association, however, was not analyzed in multivariable analysis.

Interestingly, Smagula et al. also described increased stage 2 sleep (but not decreased SWS) associated with depressive symptoms among older men in a community-dwelling sample[59]. They interpreted their result as a sign of accelerated age-related change in the sleep structure among this population. They also highlighted that the severity of depressive symptoms and the lack of treatment-seeking behaviour of these participants were different from depressed in-patients. According to their

opinion[59], these differences might contribute to the sleep architecture variation[60] they reported in this sample.

In fact, increased stage 2 sleep is not a characteristic feature of the sleep architecture of patients diagnosed with MD[19-21]. However, in a randomized placebo controlled trial a significant improvement of low mood in olanzapine-treated participants was associated with changes mainly in sleep continuity measures and also the duration of stage 2 sleep, but not with the change of SWS[61].

Within this kTx population, we observed a surprisingly prolonged REM latency and decreased REM sleep compared to normal values widely-used in sleep medicine[62]. According to our current analysis, the prolongation of REM sleep latency and the consequent decrease of REM percentage may be both connected with depression.

In earlier PSG studies among kTx recipients the proportion of REM sleep was variable, from normal (21.6±5.9 %; 18.9±8.3 %)[56,58] to low (14±9.2 %)[57]. REM latency was only reported in one paper (133±76 min)[57]. Interestingly, the proportion of REM sleep was also associated with declining renal function in patients with CKD, however, this association diminished after controlling for covariables[54]. Depressive symptoms were not considered in any of the previously mentioned studies.

In a recent population-based study longer REM latency was associated with depressive symptoms (also measured by the CES-D score) even after adjustment for age and sex[63]. In the work of Smagula et al. shorter REM sleep was associated with more depressive symptoms[59]. Although shortening of REM latency and more REM sleep are thought to be markers of depression, not every patient with depression is characterized by dysregulated REM sleep[19,21]. Similarly, population-based studies sometimes report no association of REM parameters with depressive symptoms[64,65].

Contrary to our expectation, we did not find a significant association between depressive symptoms and SWS among kTx recipients. Similarly, there was no association between SWS and depressive symptoms in a large community sample (n = 2,861)[59]. It is possible that the relationship between depressive symptoms and SWS is modified by unique characteristics of certain populations (such as age, comorbidities, medications, etc). The pathophysiology of the illness, metabolic changes or the impact of medications may all be causes of variations in sleep architecture[60,63] that may alter the expected patterns described in patients with MD[17,19,20]. In this respect it is also interesting to note that SWS was higher in patients on dialysis compared to pre-dialysis or transplanted patients[53,56]. These results may indicate that the modality of the renal replacement therapy or the kidney disease itself may affect SWS and the regulation of NREM sleep in some yet undefined way. It is also possible, that the lack of significant association was due to the relatively small sample size and the consequently low statistical power.

One explanation of the observed sleep architecture variations may be that a sleep-protecting mechanism is over activated during NREM sleep among kTx recipients. Such a mechanism would

preserve SWS, but also would lead to the prolonged REM latency. Altered homeostasis of SWS could be investigated with exploring sleep microstructure including analyses of spindles, K-complexes and cyclic alternating pattern[66,67].

Several limitations of our study should be considered when interpreting the results. First, this is a cross-sectional study and this prevents us to draw conclusions about causality or temporality. Second, we did not have a control group, therefore we could not compare the sleep architecture with healthy sleepers. Third, it is possible that the impaired kidney function of kTx recipients might have influenced our findings. In this regards it is important to note, that we adjusted our multivariable models for eGFR, a generally used parameter to characterize graft function. eGFR is reportedly associated with sleep structure in earlier stages of CKD[54]. Forth, we also considered sleep disorders as potential confounders while building our models. Importantly, these variables did not alter the associations we report. Additional limitations of our study design were described previously (first-night effect, the use of multiple medications)[62].

In summary, we found that increased depressive symptom severity was significantly associated with higher stage 2 sleep percentage and prolonged REM latency in kTx recipients. These results may be related to the unique characteristics of this population and may suggest that a sleep protecting mechanism is associated with depressive symptoms among kTx recipients. Additionally, the altered NREM sleep regulation could partly be connected to the loss of REM sleep. Further research is needed to better understand the complex relationship between depressive symptoms and sleep structure among kTx recipients.

Based on our findings we propose that depression among this patient population should be treated as a different subtype, and in case of pharmacological treatment the prolonged REM latency and low amount of REM sleep should be taken into consideration. Future studies are also warranted to define the most effective treatment for depression in this patient population. Furthermore, future research should also focus on whether psychotherapy targeting sleep problems would change these markers and improve depressive symptoms in kTx recipients.

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