Analysis of subjective and objective parameters among kidney transplant recipients – Association of insomnia symptoms, depressive symptoms and graft function with sleep architecture

Thesis abstract

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1. INTRODUCTION

1.1. Chronic kidney disease, kidney transplantation

Chronic kidney disease (*CKD*) is a highly prevalent condition. This may be due to a wide availability of treatment modalities such as dialysis or transplanation, as well as to the increasing prevalence of hypertension and diabetes: disorders which commonly precede CKD.

Currently, there is no treatment to cure CKD, so the progression to end-stage kidney disease *(ESKD)* means a loss of organ function. Developing ESKD deeply affects the lives of patients and their families. On one hand, patients are grateful for the chance to replace the non-functioning kidney with renal replacement therapies. However, patients are often not able to forsee the very real burden of these life-saving therapies.

There are two main modalities of renal replacement: dialysis or kidney transplantation. Since the second half of the last century, these two treatments have made it possible for patients with ESKD to live decades after the loss of their kidney function.

Kidney transplant (*kTx*) recipients have lower mortality and morbidity as well as better quality of life than dialyzed counterparts, which is why kidney transplantation is considered to be the best option as treatment of ESKD. However, morbidity is still higher and quality of life is lower among kTx recipients than in the general population. There has also been a higher reported prevalence of cardiovascular diseases, infections, and neoplasms among transplant recipients. Furthermore, poorer quality of life is considered to be associated with the invasivity of the treatment itself. Both transplantation and dialysis are highly invasive, which has significant negative effects on the quality of life of these patients.

The concept of quality of life is valuable among patients with CKD or ESKD, because standard clinical and laboratory markers are not sufficient to describe the actual and subjective condition of these patients. Assessment of quality of life is also a useful tool for comparing the different treatment modalities. It is well described in the literature that quality of life and even mortality are both associated not only with somatic factors (age, diabetes, other co-morbidities), but also with several psycho-social factors (p.e.: depression, anxiety, sleep disorders, social support, subjective perception of well-being).

1.2. Significance of sleep, sleep structure in insomnia and depression

One-third of the life of a human being is spent alseep; in adulthood, we spend six to eight hours sleeping every day. Sleep is a basic physiological need, however defining its exact function is still a challenge in science. The main functions of sleep are known to be its involvement in the development of the neural system, learning and memory consolidation, and to support wakefulness as is described in the homeostatic model of sleep/wake regulation.

While asleep, several systems of the organism experience a functional change. For example, the central nervous, respiratory, circulatory, endocrine and immune systems; metabolic regulation; and even skeletal muscles function differently during sleep. It therefore follows that any quantitative or qualitative change in the sleeping process can lead to signifcant consequences for the organism. Results from the most important research in the past two decades has shown sleep to be associated with mortality. The significance of sleep with regards to several chronic diseases is now also becoming widely noted.

In previous decades, the consensus was that sleep architecture in both insomnia and depression is different from that of healthy sleepers. Studies using polysomnography (*PSG*) and detailed EEG analysis contributed important information about the pathophysiology of both insomnia and depression, and helped in developing better therapies to improve subjective symptoms.

Diagnosis of insomnia is based on a clinical interview when the patients' subjective complaints, as well as symptoms related to the sleep problem are explored. Assessment with PSG is required only when a comorbid sleep disorder is suspected. In research settings, subjectively poor sleep quality is frequently analyzed with PSG, and in this way several sleep architecture parameters can be defined. Patients with insomnia disorder are often compared with healthy sleepers in these studies, and the results show that patients with insomnia have longer sleep onset latency, increased wake time after sleep onset, lower total sleep time, and less slow wave sleep.

Currently, the theory of hyperarousal is one of the leading concepts describing the mechanisms behind symptoms of insomnia. This theory is supported by several works showing that there is an overactivation in functioning of the subject, for example in the central nervous system. Thus, besides the previously mentioned sleep macrostructure parameters, increased wake-like (beta) EEG activity during sleep is also described in patients with insomnia.

EEG activity is measured with sleep microstructure analysis, which is a more detailed method to analyze sleep EEG than standard PSG. With power spectral analysis, the activity in different frequency bands is defined. In patients with insomnia the most important bands, which are known to differ from healthy sleepers, are beta activity (which describes the level of hyperarousal) and delta activity (which reflects the sleep regulatory homeostatic process).

The sleeping process has also gained attention for its significance among depressed patients. Subjective complaints of insomnia are very frequent among these patients, in fact such complaints are considered as one of the major symptoms of depression. Insomnia-like sleep macrostructure was observed in several PSG studies of depressed patients.

Furthermore, depressed patients often have decreased amounts of slow wave sleep and increased amount of REM (*rapid-eye movement*) sleep with shortened REM latency. REM related changes are present among 50-70 % of depressed patients, which may persist after the remission of depression, as well as increase the risk of relapse and have associations with therapeutic response.

1.3. Significance of sleep architecture, insomnia and depression among kidney transplant recipients

As previously described, complaints of both insomnia and depression are prevalent among kTx recipients. Unfortunately, most complaints remain untreated in clinical settings, despite being treatable conditions.

More recently, the significance of sleep has become a priority in somatic conditions. This may be due to recent findings of the association of sleep duration and several chronic somatic diseases, as well as mortality. Several studies suggest that sleep disorders such as insomnia, restless legs syndrome, periodic limb movements in sleep, and obstructive sleep apnea are frequent among patients with ESKD. Among dialyzed patients, there are some studies with PSG that describe sleep architecture, however there is very limited information about the objectively assessed sleep architecture among kTx recipients.

There are only three previous studies with PSG assessment of sleep among kTx recipients. These works contained relatively few patients (n_1= 9; n_2= 18; n_3= 34), and all of them focused on sleep apnea. Detailed data of sleep architecture were not presented in the results.

To the best of our knowledge, there is only one PSG study which analyzed sleep macrostructure in earlier stages of CKD. In this study, worse kidney graft function (*estimated glomerular filtrate rate: eGFR*) was associated with worse sleep quality in univariable analysis.

2. AIMS OF THE STUDY

The aim of my research was to analyze whether symptoms of insomnia or depression, and kidney graft function, are associated with sleep architecture among kTx recipients. Our study design was cross-sectional, from a relatively large study population enrolled randomly from a single center. The severity of symptoms of insomnia and depression was measured with questionnaires, and estimated graft function was determined by demographic and laboratory data. Sleep macroarchitecture was assessed by PSG in the whole sample. In a subgroup of patients, sleep microstructure was also analyzed, and the absolute spectral powers within different frequency bands were defined.

Based on the relevant scientific literature the followings were hypothesized:

2.1. Analysis of the association of insomnia symptoms with sleep macro- and microstructure:

The severity of symptoms of insomnia is associated with parameters of sleep macrostructure (longer sleep onset latency and wake time after sleep onset, less total sleep time and slow wave sleep).

The severity of symptoms of insomnia is associated with higher beta and lower delta activity in sleep microstructure.

2.2. Analysis of the association of depressive symptoms with sleep macro- and microstructure:

The severity of symptoms of depression is associated with parameters of sleep macrostructure (less slow wave sleep, more REM sleep and shorter REM sleep latency).

The severity of symptoms of depression is associated with higher beta and lower delta activity in sleep microstructure.

2.3. Analysis of the association of kidney graft function with sleep macrostructure:

Worse kidney graft function is associated with shorter total sleep time, less slow wave sleep and REM sleep.

3. METHODS

3.1. Sample of patients and data collection

Data for this analysis were obtained from the ‘‘SLeep disorders Evaluation in Patients after kidney Transplantation (*SLEPT*) study’’. Potentially eligible patients were selected from all adult transplant recipients (‘‘total clinic population’’; n = 1,214) who were regularly followed at a single outpatient academic transplant center, the kidney transplant clinic of the Dept. of Transplantation and Surgery at Semmelweis University, Budapest, Hungary.

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).

From these 150 eligible patients (‘‘kTx study sample’’), 50 individuals (33%) refused to participate. Consequently, the ‘‘kTx PSG sample’’ who underwent PSG included 100 kTx patients. Of all PSG recordings in the ’’kTx PSG sample” 56 had sufficient quality to allow sleep microstruture analysis (’’kTx EEG sample”).

Demographic and anamnestic data was collected at enrollment including age, sex, etiology of CKD, smoking, education, presence or absence of diabetes. Transplantation-related information and comorbidies (modified Charlson Comorbidity Index) were also tabulated. eGFR was calculated using the ’’4-variable” *CKD-EPI* (Chronic Kidney Disease EPIdemiology collaboration) formula. Laboratory data were extracted from the medical charts.

Before the sleep study patients received a package of validated questionnaires (including *AIS*: Athens Insomnia Scale and *CES-D*: Center for Epidemiologic Studies – Depression Scale). Patients received help from a trained assisstant if it was needed (p.e.: writing, reading difficulties, help in comprehension).

The study was approved by the Research 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 form.

3.2. Assessment of symptoms of insomnia and depression

The AIS was used to assess sleep complaints and to identify possible cases of insomnia. The AIS consists of eight items, with 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 to detect clinically significant insomnia.

We assessed depressive symptoms with the Hungarian version of the CES-D scale. This questionnaire contains 20 items (with score range 0-60) that ask participants to grade how frequently their complaints occured (rarely, 1-2 days, 3-4 days, 5-7 days) within the last week. The total CES-D score was used to describe psychological distress 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.

3.3. Polysomnography

Standard, attended overnight PSG was performed in an acoustically isolated and video-monitored sleep laboratory equipped with 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 mostly set around 22:00 and 6:00, respectively.

Recordings were manually scored by two somnologists. Sleep stages were determined in 30 sec epochs according to Rechtschaffen and Kales. Sleep macroarchitecture was characterized by the following variables: sleep onset latency (time elapsed from "lights off " to the first occurrence of sleep stage 2), total sleep time, wake after sleep onset (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 (stages 3 and 4 combined) and percentage and latency of REM (*rapid eye movement*) sleep. Respiratory events and periodic leg movements were also scored according to standard criteria.

3.4. Analysis of sleep microstructure

Sleep microstructure was analyzed with power spectral analysis. Prior to power spectral analysis EEG artefacts were removed from all EEG channels. For this purpose, EEG segments containing artefacts were visually identified and annotated on a 4-second basis by an experienced somnologist using our custom-made software (FerciosEEG, © Ferenc Gombos

2008-2016). EEG signals were subsequently exported, while the annotated segments were excluded from further analysis. Power spectral density averaged over the whole night was calculated separately for NREM (*non-REM*; stages 2, 3 and 4 combined) and REM sleep stages.

Artefact-free EEG segments of interest were concatenated and power density was calculated for central derivations (C3-Cz, C4-Cz) using Welch's periodogram method as averages over detrended Hanning windowed 4-second long epochs with 50 % overlap. Frequency-specific absolute spectral powers (in $\mu V^2/Hz$) were obtained as the integral of the cubic spline interpolated power values over the delta: 0.75-4 Hz, theta: 4-8 Hz, alpha: 8-11 Hz, sigma: 11-15 Hz, and beta: 15-25 Hz bands divided by the width of the respective band. The algorithms were based on the NumPy, SciPy, and Matplotlib libraries for scientific computing.

3.5. Clinical data

Comorbidity was assessed by the modified Charlson Comorbidity Index completed by the participant's responsible transplant physician. Information about other selected comorbid conditions (coronary artery disease, diabetes, hypertension) and medication use was obtained from the questionnaires and the patient's medical charts. Additionally, blood pressure and antropometric parameters were also measured, and information about smoking was asked at the time of the PSG assessment.

Transplantation-related information collected included current medications, transplant and dialysis ''vintage'' (time elapsed since transplantation or time spent on dialysis prior to transplantation). 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. All enrolled kTx recipients were receiving maintenance IS therapy during our study.

3.6. Statistical analysis

Statistical analysis was carried out using STATA 13.0 software. Results were presented as percentage (%), mean (±*standard deviation/SD* – normal distribution) or median (;*interquartile range/IQR* – non-normal distribution). 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 Fisher's exact test where the observation numbers were low. Correlation analysis was performed using Pearson and Spearman rank correlation analysis.

We analyzed the association between the AIS score, CES-D score or graft function versus sleep architecture parameters with multivariable linear regression. The models were built

with the sleep parameter as dependent variable and the AIS score, CES-D score or graft function as independent variable. We selected the covariables based on theoretical considerations. We used transformations to achieve normal distribution of the variables where it was necessary.

The models were built in a step-wise approach. When analysing associations with AIS or CES-D score we included at first step (Model 1) the subjective score, age, sex and graft function. At second step (Model 2) the other subjective score (CES-D or AIS, respectively) and hypnotic medication use variables were also included. When analysing association between sleep structure with graft function models were built in three steps. We included at first step (Model 1) age and sex, besides graft function. At second step (Model 2) we adjusted for AIS and CES-D scores and hypnotic medication use. At third step (Model 3) presence or absence of hypertension and diabetes were also included as covariables.

In all statistics, two-sided tests were used and $p < 0.05$ was considered statistically significant.

4. Results

4.1. Demographic data and baseline characteristics of the sample

The mean age of the study population (''kTx PSG sample") was 51±13 years, 57 % of them was male, body-mass index was 27±5 kg/m^2. Based on eGFR (54±19 ml/min/1.73m^2) patients had 3rd stage CKD. 19 % of patients had diabetes and 92 % of them hypertension, Charlson Comorbidity Index was 2;1 in the sample. Serum albumin was 40±3 g/L. Patients were taking IS medication as follows: 85 % prednisolone, 43 % cyclosporine A microemulsion formulation, 71 % mycophenolate-mofetil, 46 % tacrolimus, 12 % sirolimus and 5 % azathioprine. The median;IQT time of ESKD was 101;91 months, dialysis vintage was 18;32 months, time elapsed since transplantation was 66;83 months in the sample.

The median;IQR AIS score was 4;6 in the ''kTx PSG sample''. 16 % of the kTx recipients had high risk of insomnia based on the AIS cut-off score. 17 % of the patients were taking hypnotic medication.

The median;IQT of CES-D score was 9;11 in the sample. One fifth of the patients scored 18 or higher indicating high risk of clinically significant depression. Despite the high prevalence of depression in the sample only 2 patients were receiving antidepressant pharmacotherapy in the "kTx PSG sample". We decided to exclude these two patients from the analyses focusing on depressive symptoms.

4.2. Assessment of sleep macrostructure

Sleep latency was 15;17 min, sleep efficiency was 80;13 % in the "kTx PSG sample". Mean duration of sleep spent in the sleep laboratory resulted 6±1.3 h, wake after sleep onset was 61;47 min, the proportion of slow wave sleep was 12±8 %. The prevalence of severe obstructive sleep apnea based on the apnea-hypopnea index was 14 %, the prevalence of severe periodic limb movement disorder based on the periodic limb movement index was 16 % in the "kTx PSG sample".

4.3. Association of symptoms of insomnia with sleep macrostructure

Sleep macrostructure parameters were not associated significantly with the severity of insomnia symptoms in correlation analysis. However, there was a trend-like association between sleep efficiency and insomnia symptoms ($r= -0.179$; $p= 0.075$). Additionally, insomnia and depressive symptoms correlated significantly ($r= 0.493$; $p< 0.001$).

We analyzed the selected sleep macrostructure parameters (sleep onset latency, total sleep time, slow wave sleep, wake after sleep onset time – dependent variable) with multivariable linear regression. However, with an explorative aim we also analyzed other sleep

macrostructure parameters in multivariable analysis. After controlling for potential confounders in Model 1 (age, sex, eGFR) higher AIS score was significantly associated with less REM sleep (β: -0.217; CI: -0.415 - -0.018; p= 0.033) and longer REM latency (β: 0.234; CI: 0.027 – 0.442; p= 0.027). After additional adjustment in Model 2 (CES-D, hypnotic medication use) the association with REM sleep did not remain significant (β: -0.117; CI: -0.353 – 0.120; p= 0.328), however, REM latency was nearly significantly associated with AIS score (β: 0.235; CI: -0.008 – 0.478; p= 0.057). In Model 2 higher AIS score was significantly associated with higher proportion of slow wave sleep (β: 0.263; CI: 0.026 - 0.500; p= 0.030). AIS score was not associated with any other parameters of sleep macrostructure in the fully adjusted models.

4.4. Association of symptoms of insomnia with sleep microstructure

In the next step we analyzed the association between AIS score and absolute power spectra. The AIS score significantly correlated with the REM sigma frequency band (r= 0.287; p= 0.032) and there were trends towards a positive correlation with REM beta (r= 0.257; p= 0.055) and NREM alpha (r= 0.244; p= 0.070). The AIS score was not associated with power spectra of NREM beta, NREM delta or REM delta in the univariable analysis.

We further analyzed the association of beta and delta power spectra with the AIS score in multivariable regression models. With an explorative aim we also analyzed other frequency bands (NREM alpha and REM sigma) in multivariable analysis.

Models were built as previously, in two steps. After adjusting for covariables at first step (Model 1) AIS score was significantly associated with NREM alpha (β: 0.279; CI: 0.016 – 0.541; p= 0.038) and REM sigma (β: 0.345; CI: 0.075 – 0.614; p= 0.013) activity, however, these associations did not remain significant in Model 2. In both Model 1 and Model 2 AIS score was independently associated with higher REM beta power (Model 1: β: 0.452; CI: 0.200 – 0.705; p= 0,001; Model 2: β: 0.323; CI: 0.041 - 0.606; p= 0.026). Power spectra of NREM beta and delta or REM delta were not associated with AIS score.

4.5. Association of symptoms of depression with sleep macrostructure

In correlation analysis higher CES-D score was significantly associated with more stage 2 sleep (r= 0.203; p= 0.049), longer REM latency (r= 0.208; p= 0.045) and less REM sleep (r= -0.243; p= 0.018), but not with the proportion of slow wave sleep (r= -0.117; p> 0.05).

To assess the independent association between depressive symptoms and sleep macrostructure we utilized multivariable analysis. The selected sleep macrostructure parameters (proportion of slow wave sleep, REM sleep, and 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. At first step Model 1 was adjusted for age, sex and graft function. In this model REM sleep (β: -0.257; CI: -0.458 - -0.055; p= 0.013) and REM latency (β: 0.237; CI: 0.030 – 0.443; p= 0.025) were significantly associated with CES-D score. However, these associations did not remain significant after additional adjustment for AIS score and hypnotic medication use. Similarly, the proportion of slow wave sleep was not associated with CES-D score after controlling for covariables either (β: -0.175; CI: -0.403 – 0.052; p= 0.129). Interestingly, higher proportion of stage 2 sleep was significantly associated with depression severity independent of other covariables in the fully adjusted model (β: 0.274; CI: 0.037 – 0.511; p= 0.024).

4.6. Association of symptoms of depression with sleep microstructure

In the next step we analyzed the association between CES-D score and absolute power spectra. The CES-D score significantly correlated with NREM beta (r= 0.310; p= 0.023) and sigma (r= 0.300; p= 0.028), REM beta (r= 0.291; p= 0.033) and sigma (r= 0.208; p= 0.040) frequency bands. The CES-D score was not associated with delta power in the univariable analysis.

We further analyzed the association of beta and delta power spectra with the CES-D score in multivariable regression models. Since in the univariable analysis sigma power was significantly associated with CES-D score we decided to further analyze NREM and REM sigma bands in multivariable analysis.

Models were built as previously, in two steps. After adjusting for covariables at first step (Model 1) CES-D score was significantly associated with NREM beta (β: 0.261; CI: 0.017 – 0.505; p= 0.037) and REM beta (β: 0.329; CI: 0.079 – 0.579; p= 0.011). However, these associations did not remain significant in Model 2. In both Model 1 and Model 2 NREM sigma activity was significantly associated with CES-D score (β: 0.278; CI: 0.069 – 0.488; p= 0.010 and β: 0.252; CI: 0.023 – 0.480; p= 0.032, respectively). CES-D score was not associated with other frequency bands analyzed in multivariable analysis.

4.7. Association of kidney graft function with sleep macrostructure

In correlation analysis eGFR was not significantly associated with sleep macrostructure parameters. However, there were trend-like associations with total sleep time (r= -0.185; p= 0.071) and proportion of REM sleep (r= -0.190; p= 0.058).

We analyzed the association of eGFR (independent variable) with sleep macrostructure parameters (dependent variable: total sleep time, slow wave sleep or REM sleep) in linear regression models. At first step we adjusted the models for age and sex (besides eGFR). At

second step adjustment was performed with CES-D score, AIS score and hypnotic medication use variables. We also adjusted in a third step for the presence or absence of diabetes and hypertension. In the fully adjusted model (Model 3) worse graft function was independently associated with longer total sleep time (β: -0.357; CI: -0.583 - -0.132; p= 0.002) and higher proportion of REM sleep (β: -0.314; CI: -0.533 - -0.096; p= 0.005). Graft function was not associated with the proportion of slow wave sleep in multivariable analysis (β: -0.097; CI: -0.323 – 0.129; p> 0.05).

5. Conclusions

In the present work the association between symptoms of insomnia or depression, and kidney graft function versus objectively assessed sleep architecture was analyzed. The associations of the severity of subjective symptoms with sleep microstructure was also analyzed.

Hereby I summarize the new results:

1. Severity of symptoms of insomnia was not associated with selected parameters of sleep architecture (sleep onset latency, total sleep time, wake after sleep onset time).
2. Severity of symptoms of insomnia was associated with higher proportion of slow wave sleep. However, NREM delta activity was not associated with symptoms of insomnia.
3. Severity of symptoms of insomnia was associated with REM beta activity, but not with NREM beta activity.
4. Severity of symptoms of depression was not associated with the proportion of slow wave sleep, or with delta activity.
5. Severity of symptoms of depression was not associated with beta activity.
6. Severity of symptoms of depression was associated with the proportion of stage 2 sleep and with NREM sigma activity.
7. Severity of symptoms of depression was only associated with longer REM latency and less REM sleep in the multivariable model adjusted for age, sex and graft function. After additional adjustment these results did not remain significant.
8. Worse kidney graft function was associated with longer total sleep time and more REM sleep, but not with the proportion of slow wave sleep.

Most importantly, we would like to draw attention to the significance of sleep complaints among kidney transplant recipients and highlight that insomnia and depressive symptoms are associated with different alterations in sleep architecture than in the non-kidney disease population. Our results might also help to find the most appropriate intervention to improve sleep and subjective symptoms among this population. Furthermore, our research raises new questions about the significance of the low amount of REM sleep, as well as of the negative association between sleep duration/REM sleep and graft function. Other works are needed to replicate our findings and to better understand the clinical relevance of these results.

6. Publications of Applicant

Publications in relation to Thesis:

Ronai KZ, Szentkiralyi A, Lazar AS, Lazar ZI, Papp I, Gombos F, Zoller R, Czira ME, Lindner AV, Mucsi I, Bódizs R, Molnar MZ, Novak M. (2017) *Association of symptoms of insomnia and sleep parameters among kidney transplant recipients*. JOURNAL OF PSYCHOSOMATIC RESEARCH 99: 95-104. **IF: 2.809**

Ronai KZ, Szentkiralyi A, Lazar AS, Ujszaszi A, Turanyi C, Gombos F, Mucsi I, Bodizs R, Molnar MZ, Novak M. (2017) *Depressive Symptoms are Associated with Objectively Measured Sleep Parameters in Kidney Transplant Recipients*. JOURNAL OF CLINICAL SLEEP MEDICINE 13: 557-64. **IF: 3.429**

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