Association of inflammation and sleep disorders in kidney transplant recipients

Ph.D. thesis

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INTRODUCTION

To our knowledge there is only a few scientific information available regarding sleep disorders in kidney transplant recipients. According to the latest findings, the prevalence of sleep disorders are higher among patients with end stage renal disease (ESRD), compared to the general population. Epidemiological studies conducted in general population have shown that the prevalence of sleep disorders, especially obstructive sleep apnea (OSA) is associated with elevated cardio- and cerebrovascular morbidity and mortality. The most frequent cause of death among kidney transplant recipients is cardiovascular, but we do not know yet, whether OSA contributed to the cardiovascular death of these patients.

In a cross-sectional study (Transplantation and Quality of Life-Hungary (TransQol-HU)) our research group was the first to report estimates on the prevalence of restless legs syndrome (RLS), insomnia, and OSA in a large sample of consecutive kidney transplant recipients using validated questionnaires. The abovementioned study performed at the Department of Transplantation and Surgery of Semmelweis University found 5% prevalence of restless legs syndrome. After 4-year follow-up, the presence of RLS was associated with a higher risk of mortality among these patients. The prevalence of transplant patients with a high risk of OSA was 27%, which is similar to the prevalence found in waitlisted patients. According to the findings of our research group, the presence of high risk for OSA seems to be an independent predictor of graft loss in women with a kidney transplant. The prevalence of insomnia was 15% in waitlisted dialyzed patients, whereas in kidney transplant recipents it was 8%, similarly to the general population.

Scientific evidence suggests that partial and total sleep deprivation results in elevation of proinflammatory markers like C-reactive protein (CRP), interleukine-6 (IL-6) and tumor-necrosis faktor-α (TNF-α) in healthy individuals. It is also known, that significantly higher concentrations of proinflammatory citokines (IL-6, IL-1 and TNF-α) and acute phase proteins (like CRP) are detectable in patients with chronic kidney disease. Presence of malnutrition and inflammation is associated with elevated cardiovascular morbidity and mortality in patients on maintenance dialysis. Several factors might contribute to this association. Malnutrition-inflammation complex syndrome showed association with presence of posttransplant anemia, depressive symptoms, and quality of

life. In addition, inflammation in dialysed patients was associated with increased risk of mortality after kidney transplantation, because decreased level of serum albumin, as a marker of persisting inflammation, showed to be an independent predictor of posttransplant mortality. Furthermore, chronic inflammation was associated with worse quality of life, depressive symptoms, and risk of graft loss and mortality in kidney transplant recipients. However, we do not know, if there was any association between inflammation and presence of sleep disorders in this patient population.

According to our knowledge, there was no other study evaluating large number of kidney transplant recipents with polysomnography. Consequently, our study group designed this cross-sectional study enrolling 100 kidney transplant recipents and 50 dialyzed patients on the waiting list to evaluate sleep disorders with the gold standard method, and compare the two patient groups. We also measured serum levels of several proinflammatory markers to test our hypothesis regarding association of sleep disorders and inflammation.

My research work involved evaluation of the prevalence and correlates of sleep disorders (obstructive sleep apnea, periodic limb movements in sleep (PLMS) and insomnia) in kidney transplant recipents. In addition, I was to answer the scientific question, if there was an association between elevated serum levels of proinflammatory markers and different sleep disorders in this patient group. Finally, I tested the hypothesis, if the presence of OSA was associated with higher estimated cardiovascular and cerebrovascular risk in kidney transplant recipents.

AIMS

ASSESSMENT OF THE ASSOCIATION OF SLEEP DISORDERS (OSA, PLMS, INSOMNIA) WITH INFLAMMATION IN KIDNEY TRANSPLANT RECIPIENTS

OSA, insomnia and periodic limb movements in sleep are common sleep disorders in patients with ESRD. Furthermore, these sleep disorders reportedly contribute to higher morbidity, mortality and graft loss in ESRD patients. Inflammation is an important predictor of mortality in hemodialyzed patients and kidney transplant recipients. In dialyzed patients there are few and controversial data available about the association of inflammation and sleep disorders, and there is lack of information regarding kidney transplant recipients. Previous studies measured only one inflammatory marker, and used questionnaires to identify sleep disorders, instead of using polysomnography. The association of inflammation with sleep disorders has not been assesed in kidney transplant recipents until now. The aim of this cross-sectional study was to assess the association of different inflammatory markers with OSA, PLMS and insomnia in a random sample of kidney transplant recipients. Polysomnography was used to diagnose OSA and PLMS, and questionnaire to screen for symptoms of insomnia.
The following hypotheses were generated:

1. There is an association between the presence of OSA and proinflammatory markers (IL-6, TNF-α, CRP, white blood cell count).
2. This association remains significant after adjustment for renal function and other known factors.
3. There is an association between presence of PLMS and proinflammatory markers of the blood (IL-6, TNF-α, CRP, white blood cell count).
4. This association remains significant after adjusting for renal function, presence of OSA, parameters reflecting to iron deficiency, and other known factors.
5. There is an association between the presence of insomnia and proinflammatory markers (IL-6, TNF-α, CRP, white blood cell count) of the blood.
6. This association is independent of renal function and other known factors.

PREVALENCE AND SEVERITY OF OBSTRUCTIVE SLEEP APNEA IN KIDNEY TRANSPLANT RECIPIENTS VERSUS WAITLISTED DIALYSIS PATIENTS AND CROSS-SECTIONAL ASSESSMENT OF THE ASSOCIATIONS OF ESTIMATED CARDIO- AND CEREBROVASCULAR RISK IN TRANSPLANT AND WAITLISTED PATIENTS

The prevalence of moderate and severe OSA (apnea hypopnea index (AHI)>15) is 2-4% in the general population, and is associated with increased cardiovascular morbidity and mortality. OSA is reportedly associated with higher risk of stroke, hypertension, diabetes mellitus, congestive hearth failure, arrhythmias and the metabolic syndrome and also with fatal and non-fatal cardiovascular events. Previous studies have shown high prevalence of OSA (16-54%) in patients with chronic kidney disease. OSA showed to be more common in hemodialyzed patients than in general population. Although OSA may contribute to the increased cardiovascular risk seen in transplant patients, consistent information about OSA in kidney transplanted recipients is scarce. Earlier we found in a survey study, that the prevalence of high risk of OSA was about 30% both in waitlisted and in transplant patients. A case series indicated that AHI did not change after transplantation in 73% of the patients. On the other hand, a study from Italy reported that 22% of renal transplant recipients had a respiratory disturbance index above 5/hour, which was similar to results seen in the general population. This cross-sectional study was designed to determine the prevalence and clinical correlates of OSA in a large, randomly selected sample of kidney transplant recipients using polysomnography. Hypotheses as follows:

1. The prevalence of OSA is similarly high in transplant and waitlisted patients.

2. Similarly to the general population, the presence of OSA is associated with the presence of therapy resistent hypertension.

3. The presence of severe OSA is associated with higher estimated cardio- and cerebrovascular risk in both patient groups.

METHODS

ETHICAL APPROVAL

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

STUDY SAMPLE

Transplant patient group

For this study ("SLeep disorders Evaluation in Patients after kidney Transplantation (SLEPT) Study") potentially eligible patients were selected from all prevalent adult transplant patients (n=1,214) who were regularly followed at a single outpatient transplant center on 31th December, 2006. After applying exclusion criteria (transplant received within less than 3 months, active and acute respiratory disorder, acute infection, hospitalization within 1 month, surgery within 3 months) 1,198 patients remained. From this base population we randomly selected and approached 150 patients using the simple random sampling strategy offered by SPSS 15.0. Of the 150 eligible patients 50 individuals (33%) refused to participate. Consequently, the final study population included 100 trasnplant patients. The basic characteristics (age, gender, eGFR, hemoglobin, serum albumin) of the 100 participating transplant patients were similar to the characteristics of the total clinic population.

Waitlisted patients group

All (n=100) eligible waitlisted dialysis patients who were treated at the four largest dialysis centers in Budapest (listed with the above transplant center) were asked to participate. From the 100 patients 50 (50%) individuals refused to participate in the study. The final study sample consisted of 50 waitlisted patients. Among these patients, 47 was on hemodialysis, and three were on peritoneal dialysis treatment. Details of medical history such as age, gender, level of education, tobacco use and etiology and history of chronic kidney disease (CKD) were collected at enrolment.

DATA COLLECTION

Demographic data and details of medical history were collected at enrollment when information about age, gender, etiology of CKD, transplantation-related data including immune suppressant medication use and co-morbidities including the modified Charlson Comorbidity Index (CCI) were obtained. Estimated glomerular filtration rate (eGFR) was calculated using the "4-variable" Modification of Diet in Renal Disease (MDRD) study formula. Laboratory data were extracted from the charts and from the electronic laboratory database of the hospital. The following laboratory parameters were tabulated: white blood cell count, hemoglobin (Hb), serum CRP, albumin, creatinine and blood urea nitrogen (BUN). In the sleep laboratory, participants were asked to fill out a validated questionnaire package including Athens Insomnia Scale (AIS) to assess sleep complaints and identify possible cases of insomnia.

COMORBIDITIES

Information about cardiovascular disease and hypertension was collected from patients' charts. Before polysomnography, anthropomethric parameters, history of smoking, and blood pressure of the patients were tabulated. Presence of atrial fibrillation was detected during polysomnography. Regarding comorbidities, physicians filled out the modified Charlson Comorbidity Index (CCI), which is a weighted scoring system based on the presence or absence of each of 17 variables. Earlier it has been reported that the CCI was a predictor of survival in kidney transplant patients. Since one of the variables is the presence of moderate to severe renal disease, the minimum score for all patients with ESRD is 2. Thus, in patients with ESRD scores range from 2 to a possible maximum of 33.

POLYSOMNOGRAPHY

Standard, attended overnight polysomnography was performed in acustically isolated and video monitored sleep laboratory with four individual suits in tour sleep laboratory. Recordings were manually scored by two somnologists. Sleep stages were determined in 30s epochs according to Rechtschaffen and Kales.

DEFINITION AND CLASSIFICATION OF OBSTRUCTIVE SLEEP APNEA

Apnea was defined as the absence of airflow for more than 10s; hypopnea was defined as a clearly discernible reduction in airflow for more than 10s associated with an arousal and/or reduction in oxygen saturation >3%. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. "Average oxygen saturation" was calculated from the oxygen saturation values measured during sleep. Patients were defined apneic if: mild: $5 \leq AHI < 15$; moderate: $15 \leq AHI < 30$ and severe: $AHI > 30$. Similarly to previous publications the term 'OSA' refers to moderate or severe apnea ($AHI \geq 15$) in this study.

DEFINITION AND CLASSIFICATION OF PERIODIC LIMB MOVEMENT IN SLEEP

PLMS was defined by the following criteria: limb movement (LM) duration: 0.5-5s; inter-movement interval: 5-90s; and separation criteria for LMs occurring in both legs: more than 5s between onsets. A PLMS cycle consisted of at least four consecutive LMs. The periodic limb movement index (PLMI) was defined as the number of LMs per hours during sleep. We defined PLMS if $PLMI \geq 15$.

ASSESSMENT OF INSOMNIA

The Athens Insomnia Scale (AIS) was used to assess sleep complaints and identify possible cases of insomnia. The AIS consists of 8 items (score range 0-24, with higher scores indicating worse sleep). The first 5 items cover night-time symptoms of insomnia (difficulty initiating sleep; difficulty maintaining sleep; early morning awakening), and 3 items probe daytime consequences of disturbed sleep (well-being, functioning capacity and daytime sleepiness). Subjects were asked to grade the severity of these 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. The English version of the AIS had been previously translated and validated by our group. Internal consistency of the Hungarian version of the AIS was excellent and test-retest validation showed good overall reproducibility.

TRANSPLANTATION AND DONOR RELATED DATA; IMMUNOSUPPRESSIVE THERAPY

Transplantation related information was collected including current medications, transplant and dialysis "vintage" (i.e. time elapsed since transplantation or since the initiation of dialysis treatment), time spent on dialysis prior to transplantation, type of transplantation (deceased donor or living donor related), history of cumulative acute rejection, HLA mismatch, titer of pretransplant panel reactive antibodies (PRA), cold ischemic time (CIT), age and gender of donor and history of delayed graft function. Time elapsed since the initiation of the first treatment for ESRD (cumulative ESRD time) was also calculated. Standard maintenance immunosuppressive therapy generally consisted of prednisolone, either cyclosporine A microemulsion formulation (CsA) or tacrolimus, combined with mycophenolate-mofetil (MMF) or azathioprine, everolimus or sirolimus.

MEASUREMENT OF PROINFLAMMATORY CYTOKINES

Serum samples were collected at the time of the baseline assessment and stored at -70 C^{o} for future use. From these samples high sensitivity interleukine-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels were measured using immunoassay kits based on solid-phase sandwich enzyme linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN).

ESTIMATION OF CARDIOVASCULAR AND CEREBROVASCULAR RISK

The ten-year coronary heart disease risk was estimated for all transplant patients using the Framingham score (calculated with total cholesterol). Similarly, the ten-year estimated risk of stroke was calculated according to the modified version of the Framingham Stroke Risk Profile.

DEFINITION OF THERAPY RESISTENT HYPERTENSION

Blood pressure was measured in the clinic three times after ten minutes rest. The average of the three measurements was tabulated. Data

regarding antihypertensive drugs taken by the patients were collected in all cases. The group of patients who took three or more anti-hypertensive drugs was defined as having therapy resistent hypertension.

STATISTICAL ANALYSIS

Statistical analyses were carried out using the STATA 11.1 software. Results are presented as percentage, mean (±standard deviation, SD) or medians (interquartile range, IQR). Continuous variables were compared using Student's t-test or the Mann-Whitney U test and categorical variables were analyzed with chi-square test. Kruskal-Wallis test was used to analyze the relationship between continuous and categorical variables. Correlation analyses were performed using Spearman's correlation. For multivariate analysis, logistic regressions were applied. Variables were included in the multivariate models based on theoretical considerations and also on the results of the bi-variate analyses. Variance influence factors (VIF) were used to indicate colinearity between independent variables. In all statistics, two-sided test were used and the results were considered statistically significant if p was less than 0.05.

As many of my results are negative, I had to make sure to avoid the type II error. Consequently, based on clinical experience, the clinically minimally important difference in inflammatory markers was defined: CRP at least 5 mg/l; IL-6 at least 1 ng/l; TNF-α at least 0.5 ng/l; serum albumin at least 1 g/l; and white blood cell count at least $1x10^3$/l. Sample size estimation was performed to assess the number of patients needed to detect these minimally important differences. All of these numbers were less than my sample size.

In order to determine if the association between inflammatory markers and sleep disorders was independent of other clinical and laboratory parameters, linear and logistic regression analyses were performed. Variables were built into the models in case they had shown significant association with the presence of sleep disorders in the bivariate analyses. Furthermore, adjustment was made for variables that showed association with sleep disorders according to the literure and our earlier findings. In the analysis of OSA and inflammatory markers, adjustment was made for age, gender, hemoglobin, body mass index (BMI) and estimated GFR. In the model of PLMS and inflammatory markers we adjusted for gender, age, presence of diabetes, iPTH,

estimated GFR and iron deficiency (per definition: transferrin saturation<20% and/or ferritin < 100 microg/L). In the model of insomnia and inflammatory markers age, gender, hemoglobin, Charlson Comorbidity Index and estimated GFR were used as covariables.

In order to answer the question, which factors best predict the presence of OSA and the patients' AHI, different models were designed, based on literature and the bivariate associations. When AHI as dependent variable showed a skew distribution, even after trying out different methods to transform to normal distribution, negative binomial regression analysis was used. The independent association of AHI was assessed with the following covariables: age, gender, albumin, hemoglobin, abdominal circumference, intake of three or more antihypertensive drugs. To assess the independent predictors of moderate and severe OSA (AHI≥ 15/óra) binary regression analysis was performed including the same covariables that were used in the previous multivariate anyalsis. As a sensitivity analysis, the same multivariate analyses was repeated in the total study population (including both transplant and waitlisted patients).

RESULTS

1. ASSESMENT OF THE ASSOCIATION BETWEEN INFLAMMATION AND SLEEP DISORDERS

DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS OF THE SAMPLE

Of the 150 eligible patients 50 individuals (33%) refused to participate. Consequently, the final study population included 100 transplant patients. There were no significant differences regarding age and gender between participants and those who refused to participate. The basic characteristics (age, gender, eGFR, hemoglobin, serum albumin) of the 100 participating transplant patients were similar to the characteristics of the total clinic population. The mean age was 51±13 years, 43% were female and the prevalence of diabetes was 19%. The mean±standard deviation (SD) of serum albumin and white blood cell count and the median and IQR of serum IL-6, serum CRP and TNF-α was 40.2±3.4 g/l, 8.2±2.4x103/l, 2.0 (1.2-3.2) ng/l, 3.5 (1.5-5.9) mg/l and 1.9 (1.4-2.7) ng/l, respectively. Eighty-five percent of the transplant patients were taking steroids, 43% were administered cyclosporine, 71% were on mycophenolate mofetil, 46% of the patients were administered tacrolimus and 5% were on azathioprine. Only 1% and 12% of the patients took everolimus and sirolimus, respectively. Six percent of transplant patients had at least one previous transplantation.

PREVALENCE AND CORRELATES OF OBSTRUCTIVE SLEEP APNEA

Twenty-five percent of our patients had OSA. We found no significant difference in the levels of inflammatory markers between patients with versus without OSA. The percentage of men was significantly higher in the OSA positive group. Patients with OSA had significantly higher BMI and hemoglobin level. All other parameters were similar between the two groups. AHI showed a significant association with white blood cell count (rho=0.23), and weak (rho<|0.15|), non significant correlations with the other inflammatory markers. In a sensitivity analysis we have examined whether the gender has a modifying effect on our results. I found no association between inflammatory markers and OSA neither in male nor in female patients.

PREVALENCE AND CORRELATES OF PERIODIC LIMB MOVEMENTS IN SLEEP

Twenty-seven percent of our patients had PLMS. Patients with and without PLMS had similar values of all measured inflammatory markers. The percentage of diabetic patients was significantly higher among patients with versus without PLMS. All other parameters were similar between the two groups. Additionally, PLM index showed weak (rho<|0.15|), non significant correlations with all markers of inflammation. The association between inflammatory markers and PLMS was similar in men and women in a sensitivity analysis within gender strata.

PREVALENCE AND CORRELATES OF PRESENCE OF INSOMNIA

Sixteen percent of our patients suffered from insomnia symptoms. The serum IL-6 level was significantly higher in patients with insomnia (AIS>=10) than in non-insomniacs (median (IQR): 3.2 (2.6-5.1) vs. 1.7 (1.2-2.9) ng/l; p=0.009). The levels of other inflammatory markers were similar in the two groups. Insomniacs were older and had significantly higher CCI compared to patients without insomnia. The usage of the sleep pills was significantly higher in insomniacs than patients without insomnia. All other parameters were similar between the two groups. AIS showed a weak (rho<|0.20|), non significant correlation with all inflammatory markers. Gender differences were examined, and IL-6 levels were higher (median (IQR): 4.3 (2.7-6.3) vs. 1.4 (1.0-2.4) ng/l; p=0.02) and serum albumin levels (mean±SD: 38.4±3.1 vs. 40.8±2.7 g/l; p=0.03) were lower in women with insomnia versus without insomnia. Among men we observed no such differences.

MULTIVARIATE ANALYSIS

A logistic regression analysis was used to determine the associations between the presence of sleep disorders and inflammatory markers. The examined inflammatory markers were not associated with the presence of any of the three sleep disorders, neither in unadjusted, nor in the fully adjusted binary logistic regression models.

2. PREVALENCE AND SEVERITY OF OBSTRUCTIVE SLEEP APNEA IN KIDNEY TRANSPLANT RECIPIENTS VERSUS WAITLISTED DIALYSIS PATIENTS AND CROSS-SECTIONAL ASSESSMENT OF THE ASSOCIATIONS OF ESTIMATED CARDIO- AND CEREBROVASCULAR RISK IN TRANSPLANT AND WAITLISTED PATIENTS

BASELINE CHARACTERISTICS OF THE WAITLISTED AND TRANSPLANT PATIENT GROUPS

Of the 250 eligible patients 100 (33%) kidney transplant recipients and 50 (50%) waitlisted dialysis patients refused to participate. Consequently, the final study population included 100 transplant and 50 waitlisted patients. There were no significant differences regarding age and gender between participants and those who refused to participate. Basic characteristics of the two patient groups were similar. The distribution of the underlying kidney diseases was also similar in the two groups, except for the proportion of chronic glomerulonephritis, which was significantly smaller in the transplant group (27% vs 42%; p=0.048).

PREVALENCE AND SEVERITY OF OBSTRUCTIVE SLEEP APNEA IN KIDNEY TRANSPLANT RECIPIENTS VERSUS WAITLISTED DIALYSIS PATIENTS

43% of the transplant and 54% of waitlisted patients had OSA (AHI>5) (p=NS). The prevalence of mild, moderate and severe OSA was similar between the transplant and waitlisted groups: 18%, 11%, 14% in the transplant group and 28%, 16%, 10% in the waitlisted group, respectively.

CORRELATES OF OSA IN THE KIDNEY TRANSPLANT RECIPIENT GROUP

The prevalence of moderate and severe OSA among transplant patients was 25%. The percentage of males was significantly higher among patients with versus without OSA. Patients with versus without OSA had significantly higher BMI, neck- and abdominal circumference. The abdominal circumferences in the groups formed by severity of OSA were: 92±14 cm in patients without OSA; 103±12 cm in patients with mild; 105±13 cm with moderate and 108±11 cm with severe OSA (p<0.001; Kruskal-Wallis test).

I did not find any association between OSA and the level of education, tobacco use or age. The Charlson Comorbidity Index score, eGFR, serum albumin and CRP levels were similar in the groups with versus without OSA. Hemoglobin was significantly correlated with AHI and was higher in apneic patients.

The median transplant vintage, the median dialysis vintage and cumulative end stage renal disease time were all similar in patients with versus without OSA. Donor characteristics (gender, type and age) and transplant related variables (cold ischemic time, cumulative acute rejection rate, PRA, DGF and HLA mismatches) were similar in patients with versus without OSA. None of the immunosuppressive medications was significantly associated with the presence of OSA.

TREATMENT WITH THREE OR MORE ANTIHYPERTENSIVE DRUGS

The proportion of transplant patients treated with three or more anti-hypertensive drugs was significantly higher in the OSA group (56% vs 31%; $p=0.022$). Moreover, the percentage of patients taking three or more anti-hypertensives was 26%, 44%, 64% and 50% in the groups with $AHI<5/h$, $5/h \leq AHI<15/h$, $15/h \leq AHI<30/h$ and $AHI>30/h$, respectively ($p<0.05$). In spite of taking significantly more anti-hypertensives, the average systolic blood pressure was still higher in OSA versus non OSA patients (147±21 mmHg vs 139±18 mmHg; $p=0.059$).

ESTIMATED CORONARY HEART DISEASE RISK AND ESTIMATED STROKE RISK

In the transplant group the ten-year estimated coronary heart disease risk (based on the Framingham score) and the ten-year estimated stroke risk (based on the modified Framingham stroke risk profile) were twice as high in the OSA versus non-OSA patients.

CORRELATES OF APNOE-HYPOPNOE INDEX

Although the presence of OSA showed no correlation, AHI, however, was significantly correlated with age. Furthermore, AHI showed a moderate association with BMI, neck- and abdominal circumference. Finally, AHI significantly correlated with hemoglobin levels.

MULTIVARIATE ANALYSIS

Independent predictors of AHI

A negative binomial regression analysis was used to determine the independent associations between AHI and the following variables: age, gender, albumin, hemoglobin, abdominal circumference and the use of three or more antihypertensive drugs. In this analysis only age and abdominal circumference remained as independent predictors of AHI.

Independent predictors of moderate and severe OSA

In a binary logistic regression model (Nagelkerge R Square=0.231) only abdominal circumference (OR 1.043, 95% CI 1.000-1.088; p=0.05) was independently associated with the presence of moderate–severe OSA after adjusting for the same covariables used in the previous multivariable model. Qualitatively similar results were found when these regression analyses were repeated in the total study population (including both transplant and waitlisted patients). The type of renal replacement therapy was not associated with AHI or with the presence of moderate-severe OSA in these models.

Indepenedent predictors of estimated cardio -and cerebrovascular risk

The average overnight oxygen saturation was inversely associated with both the estimated ten year stroke risk (beta=-0.196, p=0.025) and the estimated ten year coronary heart disease risk (beta=-0.256, p=0.006) in linear regression models after adjustment for gender, eGFR and the Charlson Comorbidity Index score.

CONCLUSION

In this study I assessed the prevalence of obstructive sleep apnea, periodic limb movement in sleep and insomnia in a large sample of kidney transplant and waitlisted patients using the gold standard polysomnography. I assessed the association of inflammatory markers with the abovementioned sleep disorders. I also tested if there was an association of sleep apnea with therapy resistent hypertension and 10-years estimated cardio- and cerebrovascular risk.

My own and original contributions to the science are the following:

1. There was no association between inflammatory markers (IL-6, TNF-α, CRP, white blood cell count) and the presence of obstructive sleep apnea.

2. In multivariate analysis, after adjusting for renal function and other known co-variables (age, gender, hemoglobin, BMI) there was no association for the presence of OSA with the measured inflammatory markers.

3. There was no association between inflammatory markers (IL-6, TNF-α, CRP, white blood cell count) and the presence of PLMS.

4. In the multivariate model, after adjusting for renal function and other known factors (age, gender, diabetes, iPTH, iron deficit), there was no association of the presence of PLMS with the measured inflammatory markers.

5. There was significant association between serum IL-6 levels and insomnia. This association was not significant in case of other inflammatory markers (TNF-α, CRP, white blood cell count). Serum IL-6 levels were higher in women with versus without insomnia. This association was present only in women, but not in men.

6. The association between presence of insomnia and serum IL-6 level disappeared after adjusting for renal function and other known factors (age, gender, hemoglobin, CCI) in the multivariate model.

7. I found, that the prevalence of OSA was similarly high among waitlisted and kidney transplant patients.

8. The prevalence of OSA was associated with therapy resistant hypertension in kidney transplant recipients, similarly to the general population.

9. Finally, the 10 years estimated risk of cardiovascular disease and stroke was two times higher in kidney transplant patients with OSA compared to those without OSA.

SUMMARY

In patients on dialysis available data regarding the association of inflammation with sleep disorders are controversial. There were no data available in this field in kidney transplant recipents. In this cross-sectional study ("SLeep disorders Evaluation in Patients after kidney Transplantation (SLEPT) Study") enrolling 100 kidney transplant recipients I assessed the associations of proinflammatory markers with three different sleep disorders using polysomnography for the diagnosis of OSA and PLMS. The Athens Insomnia Scale was used to detect patients with symptoms of insomnia. The levels of the following proinflammatory markers were measured: CRP, serum albumin, interleukine-6, TNF-α and white blood cell count. I have found no association between the presence of sleep disorders and the level of inflammatory markers in kidney transplant recipents.

The SLEPT study was the first to report on the prevalence of OSA diagnosed with polysomnography in kidney transplant and waitlisted patients on maintenance dialysis. The prevalence of OSA proved to be high in both patient groups. The blood pressure in kidney transplant patients who also had OSA was set out to be high despite of taking more antihypertensive drugs. Furthermore, according to our calculations the estimated ten-year coronary heart and stroke risk was twice as high in transplant patients with OSA versus patients without OSA. The results of this study pointed out the relevance and necessity of screening for obstructive sleep apnea as part of the routine workup in kidney transplant recipients, as OSA contributes to the patients' higher cardio- and cerebrovascular risk.

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