Transplantation

Chronic Insomnia in Kidney Transplant Recipients

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• ***Background:*** **Recent studies confirmed that sleep disorders have a significant impact on various aspects of health in patients at different stages of chronic kidney disease. At the same time, there is an almost complete lack of information on the prevalence and correlates of insomnia in kidney transplant recipients.** ***Methods:*** **In a cross-sectional study, the Athens Insomnia Scale was used to assess the prevalence of insomnia in a large sample of kidney transplant recipients compared with wait-listed dialysis patients and also a matched group obtained from a nationally representative sample of the Hungarian population.** ***Results:*** **The prevalence of insomnia was 15% in wait-listed patients, whereas it was only 8% in transplant recipients ($P < 0.001$), which, in turn, was not different from the prevalence of this sleep problem in the sample of the general population (8%). Prevalences of insomnia in the transplant group were 5%, 7%, and 14% for the groups with glomerular filtration rates (GFRs) greater than 60 mL/min (>1.00 mL/s), 30 to 60 mL/min (0.50 to 1.00 mL/s), and less than 30 mL/min (<0.5 mL/s), respectively ($P < 0.01$). However, estimated GFR was no longer associated significantly with insomnia in the transplant population after statistical adjustment for several covariates. In a multivariate model, insomnia was significantly and independently associated with treatment modality (transplantation versus wait listing), as well as the presence of depression, restless legs syndrome, and high risk for obstructive sleep apnea syndrome, and with self-reported comorbidity.** ***Conclusion:*** **The prevalence of insomnia was substantially less in the transplant group than in wait-listed dialysis patients and similar to that observed in the general population. Because this condition potentially is treatable, attention should be directed to the appropriate diagnosis and management of insomnia in the kidney transplant recipient population.** ***Am J Kidney Dis*** **47:655-665.**

INDEX WORDS: Chronic insomnia; sleep disorders; renal transplantation; chronic kidney disease.

RECENTLY, IT INCREASINGLY has become appreciated that disorders of sleep and wakefulness are prevalent and have a significant impact on different aspects of health in patients receiving maintenance dialysis and also patients with chronic kidney disease in the predialysis stage.[1-6] At the same time, there is an almost complete lack of information on the prevalence and correlates of insomnia in kidney transplant recipients. In this study, we wanted to determine whether the prevalence of chronic insomnia in kidney transplant recipients is different from that observed in wait-listed dialysis patients and the general population. We also wanted to explore the demographic and clinical factors associated with insomnia in the transplant population.

Insomnia is characterized by difficulty falling asleep (sleep-onset insomnia), difficulty staying asleep (sleep-maintenance insomnia), or poor sleep quality (nonrestorative sleep).[7,8] These sleep problems may lead to impaired daytime functioning, tiredness, fatigue, and sleepiness. The presence of insomnia was associated repeatedly with im-

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paired quality of life,[1,6,9,10] increased morbidity and mortality,[11,12] and increased use of health care resources.[9,13]

Earlier epidemiological studies used different approaches and instruments to define chronic insomnia, resulting in widely different estimates (6% to 50%) of the prevalence of the condition.[7,8] Recently, instruments based on diagnostic criteria outlined by either the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (SLEEP-EVAL),[14-17] or the *International Statistical Classification of Diseases, 10th Revision* (Athens Insomnia Scale [AIS]),[18,19] were developed and validated. Data obtained with these instruments in large epidemiological studies suggested a similar 6% to 9% prevalence in the general adult populations in different countries. The prevalence of sleep problems in patients on maintenance dialysis therapy is reported to be close to 50% by using various, sometimes nonstandard, instruments.[1,5,6] Recently, Iliescu et al,[2] using the Pittsburgh Sleep Quality Index, reported "poor sleep" in 53% of patients with chronic kidney disease in the predialysis stage.

Renal transplantation partially restores renal function and alleviates many uremic symptoms and complications. As a consequence, sleep problems may be less prevalent in transplant recipients than in patients treated with maintenance dialysis. At the same time, there are several biological, psychological, and social factors that may predispose this particular patient group to develop insomnia. Immunosuppressive medications may have a negative effect on sleep.[20] Comorbidity, depression, anxiety, and stress also may contribute to an increased prevalence of sleep problems. Furthermore, the presence of chronic medical conditions, such as chronic renal disease, and also the effects of different medications may alter the sociodemographic or clinical correlates of sleep problems, just as for depression in dialysis patients.[21,22] The only report analyzing sleep quality, a somewhat similar concept to insomnia, in kidney transplant recipients recently was published by Sabbatini et al.[23] These investigators found that sleep quality, measured by using the Pittsburgh Sleep Quality Index, was significantly worse in a large sample of renal transplant recipients than in healthy subjects. The proportion of "poor sleepers" was remarkably high, 52.5%, in the transplant group. However, the prevalence of insomnia in the renal transplant population is not known.

In this cross-sectional study, we assess the prevalence of insomnia by using the AIS, a self-reported questionnaire based on diagnostic criteria for chronic insomnia outlined by the *International Statistical Classification of Diseases, 10th Revision*, in a large sample of kidney transplant recipients. We compare the prevalence of insomnia in the transplant group with a similar group of wait-listed dialysis patients, as well as with a matched group obtained from a nationally representative sample of the Hungarian population. Furthermore, by using bivariate and multivariate analysis, we determine sociodemographic and clinical factors associated with overall sleep quality and the presence of chronic insomnia.

METHODS

Sample of Patients and Data Collection

All patients 18 years or older (n = 1,067) who were followed up regularly at a single kidney transplant outpatient clinic at the Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary, were approached to participate in a cross-sectional study of sleep and mood disorders and health-related quality of life in renal transplant recipients (Transplantation and Quality of Life-Hungary Study [TransQol-Hu Study]).[24,25] All patients had received a cadaveric renal transplant between 1977 and 2002. Data collection was performed between August 2002 and February 2003. Furthermore, all wait-listed dialysis patients receiving dialysis in Budapest (n = 214; listed with the named transplant center) also were asked to participate.

Sociodemographic information and details of medical history were collected at enrollment when information about age, sex, cause of chronic kidney disease, and presence or absence of diabetes and other comorbidities was obtained. Patients completed a battery of validated questionnaires (including the AIS,[18,19] Berlin Questionnaire,[26] Center for Epidemiologic Studies-Depression [CES-D] Scale,[27] and Restless Legs Syndrome [RLS] Questionnaire[28]) during dialysis sessions or while waiting for their regular follow-up visit at the transplant center.

Laboratory data were extracted from patients' charts and the electronic laboratory database at the hospitals. Serum hemoglobin, serum creatinine, and serum albumin levels were tabulated. Estimated glomerular filtration rate (eGFR) was calculated by using the abbreviated Modification of Diet in Renal Disease formula.[29]

Transplant-related data extracted from medical records included date of transplantation, medications (including current immunosuppressive medications), and "transplant vintage," ie, time elapsed since transplantation.

An age- and sex-matched sample of 2,034 individuals was obtained from the database of a separate study, the Hungaro-

study 2002,[13,30] which was conducted concurrently with the TransQoL-HU Study. Hungarostudy 2002 was a cross-sectional survey enrolling a large nationally representative sample of the Hungarian population. As a door-to-door survey, interviews were carried out by community nurses in the homes of 12,643 persons. The nurses had received appropriate training before the study commenced. Information on basic sociodemographic characteristics (sex, age, level of education, occupation, and marital status) was obtained in the survey. The AIS was included in the battery of questionnaires of Hungarostudy 2002.

Both studies were approved by the Ethics Committee of Semmelweis University. Before enrollment all study participants received detailed written and verbal information regarding the aims and protocol of the study and signed informed consent.

Assessment of Insomnia and Other Sleep Disorders

The AIS was used to assess sleep symptoms and identify possible cases of insomnia[8,19] in both studies (TransQoL-HU Study and Hungarostudy 2002). The AIS consists of 8 items (score range, 0 to 24; higher scores indicate worse sleep). The first 5 items cover nighttime symptoms of insomnia (difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening), and 3 items probe daytime consequences of disturbed sleep (well-being, functioning capacity, and daytime sleepiness). Subjects are asked to grade the severity of these symptoms (absent, mild, severe, and very severe) only if the particular symptom occured at least 3 times/wk during the last month. A recent publication suggested that in epidemiological studies, a cutoff score of 10 provides acceptable sensitivity and specificity to detect clinically significant insomnia.[18] The English version of the AIS was 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.[13]

For a more detailed assessment, we also analyzed individual insomnia symptoms; that is, difficulty initiating sleep; difficulty maintaining sleep, defined as either frequent awakenings or early morning awakening; and nonrestorative sleep.[7,8] These analyses were based on the presence or absence of the individual sleep symptoms or negative daytime consequences of inadequate sleep, assessed by means of individual items of the AIS.

Symptoms of RLS were identified by using the RLS Questionnaire[24,25,31] completed by the patients.

Symptoms of obstructive sleep apnea syndrome were assessed by using the Berlin Questionnaire,[26] which evaluates risk status for sleep apnea. Based on results of the Berlin Questionnaire, patients were classified as having a high or low risk for obstructive sleep apnea.

Assessment of Depression

The Hungarian version of the CES-D Scale[27] was translated according to a recommended procedure[32] and has undergone psychometric validation by our team in Hungarian hemodialysis and kidney transplant patients (M. Novak, G. M. Devins, K. Mah et al, in preparation). Our data suggested that the Hungarian CES-D Scale is a reliable tool to measure psychological distress and/or depression in different chronic kidney disease populations.

Self-Reported Comorbidity

Patients were asked to report if they experienced any of the following comorbid conditions: heart disease, vascular disorder, bone disease, lung disorder, eye disorder, paresthesias, diabetes mellitus, or "other conditions." Self-reported comorbidity score was calculated by summing the number of comorbid conditions reported by patients.[25,33]

Immunosuppressive Therapy and Use of Hypnotics in Transplant Recipients

Standard immunosuppressive therapy generally consisted of prednisolone and either cyclosporine A (Neoral; Novartis, Basel, Switzerland) or tacrolimus, combined with mycophenolate mofetil, azathioprine, or rapamycine.

Information on regular use of hypnotics also was collected and tabulated.

Statistical Analysis

Statistical analysis was carried out using SPSS 12.0.1 software (SPSS Inc, Chicago, IL), except for the negative binomial regression analysis, which was carried out using SAS 8.2 statistical software (SAS Institute, Cary, NC) by using the general model procedure (negative binomial regression analysis). Continuous variables were compared by using Student *t*-test or Mann-Whitney *U* test, and categorical variables were analyzed by using chi-square test or Fisher exact test, as appropriate. Analysis of variance between-group testing with Bonferroni correction or the Kruskal-Wallis test for data with non-normal distribution was used to analyze relationships between continuous and categorical variables. Correlation analysis was performed using Spearman correlation analysis. For multivariate analysis, logistic regression was used to analyze factors significantly associated with the presence of insomnia. To analyze factors independently predicting AIS score, negative binomial regression was used because distribution of scores deviated substantially from normal distribution.

RESULTS

Data for insomnia were not available because of refusal or inappropriate completion of the questionnaire for 17% of transplant recipients, 14% of wait-listed patients, and 6% of the matched general population sample (nonparticipants). The final sample analyzed therefore consisted of 884 transplant recipients, 183 wait-listed patients, and 1,996 individuals from the general population sample. Age and sex distribution of participants and nonparticipants were similar in all 3 groups (not shown).

Baseline characteristics of the study groups are listed in Table 1. The transplant and wait-listed groups were similar for most of the vari-

Table 1. Patient Characteristics

	General Population (n = 1,996)	Transplant Recipients (n = 884)	Wait-Listed Patients (n = 183)	*P*
Men	818 (41)	369 (42)	73 (40)	NS
Age (y)	49 ± 12	49 ± 13	49 ± 13	NS
Diabetes	NA	150 (17)	31 (17)	NS
Underlying kidney disease	NA			
Chronic glomerulonephritis		150 (17)	42 (23)	NS
Chronic pyelonephritis/tubulointerstitial disease		97 (11)	38 (21)	<0.001
Polycystic kidney disease		106 (12)	22 (12)	NS
Diabetic nephropathy		150 (17)	31 (17)	NS
Hypertensive nephropathy		71 (8)	24 (13)	0.02
Other or unknown		310 (35)	26 (14)	<0.001
Serum hemoglobin (g/dL)	NA	13.2 ± 1.9	11.3 ± 1.5	<0.001
Serum albumin (g/dL)	NA	4.2 ± 0.3	4.1 ± 0.4	NS
Dialysis or transplant vintage (mo)	NA	61 ± 45	46 ± 41	NA
Use of hypnotic agents	NA	54 (6)	12 (7)	NS
Insomnia present	168 (8)	68 (8)	27 (15)	0.007*
AIS score†	1 (5)	3 (4)	4 (5)	<0.001‡

NOTE. Values expressed as mean ± SD or number (percent) unless noted otherwise. To convert serum hemoglobin and albumin in g/dL to g/L, multiply by 10.

Abbreviations: NS, not significant; NA, not applicable.

*Insomnia prevalence is significantly greater in the wait-listed versus transplant and general-population groups.

†Median (IQR).

‡AIS scores are significantly different among all 3 groups.

ables analyzed. Mean single-pool Kt/V of wait-listed patients was 1.27 ± 0.25. Mean calculated GFR in the transplant group was 49 ± 22 mL/min (0.82 ± 0.37 mL/s).

Distribution of underlying kidney diseases was similar in the transplant and wait-listed groups, except proportions of patients with chronic pyelonephritis/tubulointerstitial nephritis and hypertensive nephropathy were significantly smaller and the proportion of patients with unknown kidney disease was significantly larger in the transplant versus wait-listed group (Table 1).

Sixty-nine percent of transplant recipients (612 patients) were administered cyclosporin A, 769 patients (87%) were administered prednisolone, 565 patients (64%) were administered mycophenolate mofetil, 157 patients (18%) were administered tacrolimus, and 105 patients (12%) were administered azathioprine. Only 20 transplant recipients (2%) were administered sirolimus.

Prevalence and Characteristics of Insomnia in Kidney Transplant Recipients

The prevalence of insomnia in wait-listed patients was 15%, whereas it was only 8% in transplant recipients ($P < 0.001$), which, in turn, was not different from the prevalence of this sleep problem in the general-population sample (8%; Table 1). However, AIS score was significantly different among the 3 groups studied (median, 4 [interquartile range (IQR), 5] versus median, 3 [IQR, 4] versus median, 1 [IQR, 5] for wait-listed patients, transplant recipients, and the general population, respectively; $P < 0.001$ for both comparisons; Table 1). Similarly, when the number of insomnia symptoms (either present or absent, according to individual AIS items) was analyzed in the 3 groups, a clear difference was seen among all groups studied; 83% in the wait-listed group, 70% in the transplant group, and 50% of general-population individuals reported at least 1 insomnia symptom ($P < 0.001$).

Maintenance insomnia (either frequent awakenings or too-early awakening) was the most frequent insomnia type in all 3 populations: 53%, 45%, and 40% of wait-listed, transplant, and general-population individuals reported at least a mild problem with sleep maintenance, respectively ($P < 0.001$; Fig 1A). The prevalence of sleep-onset insomnia was even more substantially different among the 3 populations (47% versus 28% versus 20% for wait-listed, transplant, and general-population groups, respec-

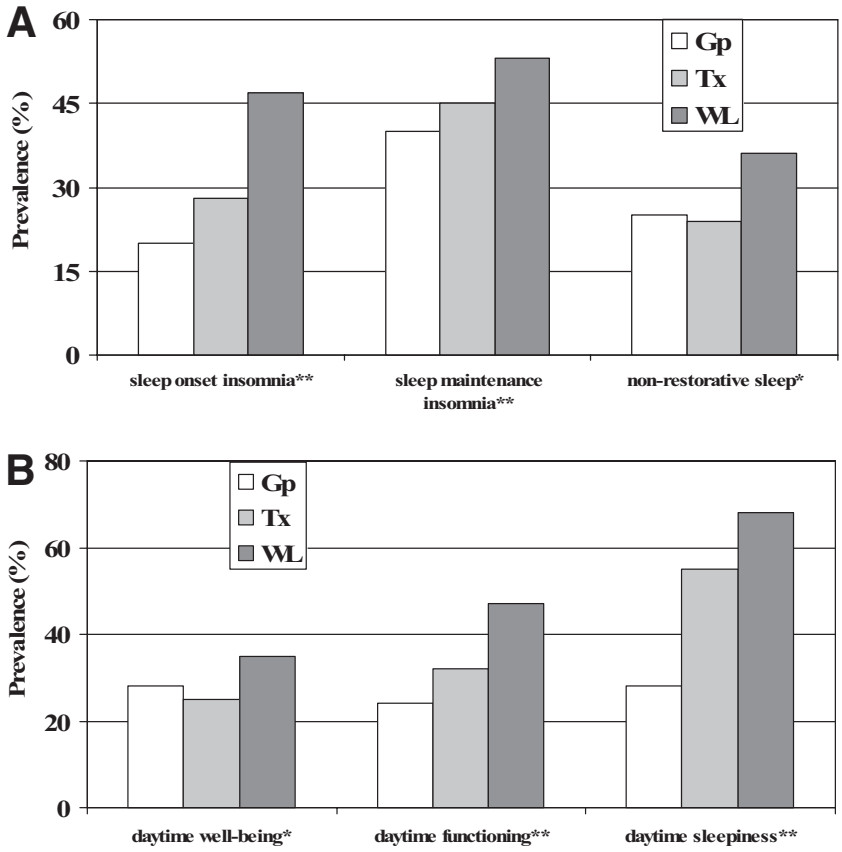

Fig 1. (A) Prevalence of insomnia symptoms in the 3 populations. *Significant difference ($P < 0.01$) between the wait-listed (WL) versus transplant (Tx) groups and WL versus general-population (Gp) groups, but not between the Tx versus Gp groups. **Significant difference among all 3 groups ($P < 0.001$). (B) Prevalence of daytime consequences of impaired sleep in the 3 populations. *Significant difference ($P < 0.01$) between the WL versus Tx and WL versus Gp populations, but not between the Tx versus Gp groups. **Significant difference among all 3 groups.

tively; $P < 0.001$). Conversely, nonrestorative sleep was similarly frequent in the transplant and general-population groups, but its prevalence was significantly greater in the wait-listed group. Daytime consequences of insomnia also showed a similar pattern (Fig 1B).

Correlates of Insomnia in Kidney Transplant Recipients

Demographic characteristics. Sociodemographic and selected clinical characteristics of patients with versus without insomnia (AIS score ≥ 10) in the kidney-transplant group are listed in Table 2. The prevalence of insomnia (10% versus 6%; $P = 0.014$) and AIS scores (median, 3 [IQR, 5] versus median, 2 [IQR, 4] for women versus men, respectively; $P = 0.05$) appeared to be higher for women transplant recipients versus men transplant recipients. The trend was similar to that observed in the general-population group (11% versus 6%; $P < 0.001$ for prevalence; median, 2 [IQR, 6] versus median, 0 [IQR, 4]; $P < 0.001$ for AIS score for women versus men, respectively). Patients with insomnia were significantly older (Table 2).

Depression. There is a well-documented bidirectional association between insomnia and depression: insomnia is an important and frequent symptom of psychological distress, but insomnia also is a precursor of depression.[11,34] The CES-D Scale was used to assess psychological distress. Median CES-D score in the transplant population was 9 (IQR, 11). AIS score correlated moderately with CES-D score ($\rho = 0.521$; $P < 0.001$). Kidney transplant recipients with insomnia had significantly higher CES-D scores than patients without the condition (median, 23 [IQR, 17] versus median, 9 [IQR, 11]; $P < 0.001$). A cutoff score of 16 on the CES-D Scale frequently has been used to suggest clinically potentially significant distress or "depression."[27] Overall, 27% of the transplant group had a CES-D score of 16 or higher. Insomnia was associated significantly with the presence of depression: the prevalence of depression was 74%

Table 2. Characteristics of Patients With or Without Insomnia in the Transplant Group

	Insomnia (n = 68)	No Insomnia (n = 816)	*P*
Age (y)	53 ± 10	48 ± 13	<0.001
Men	30 (44)	485 (59)	0.014
Transplant vintage* (mo)	60 (80)	53 (62)	0.285
Serum albumin (g/dL)	4.1 ± 0.3	4.2 ± 0.3	0.033
Serum hemoglobin (g/dL)	12.8 ± 1.8	13.2 ± 1.9	0.046
eGFR (mL/min)	42 ± 19	50 ± 22	0.004
CES-D score (depression)*	23 (17)	9 (11)	<0.001
RLS present	10 (15)	29 (4)	<0.001
High risk for obstructive sleep apnea	37 (54)	204 (25)	<0.001
No. of comorbid conditions†	3 (0-7)	2 (0-7)	<0.001

NOTE. Values expressed as mean ± SD or number (percent) unless noted otherwise. To convert serum hemoglobin and albumin in g/dL to g/L, multiply by 10; GFR in mL/min to mL/s, multiply by 0.01667.

*Median (IQR).

†Median (minimum to maximum).

in patients with insomnia and only 23% in the group without insomnia ($P < 0.001$).

Renal function and laboratory data. AIS score correlated weakly, but significantly, with eGFR ($\rho = -0.147$; $P < 0.001$). Patients with insomnia had a significantly lower eGFR than patients without the condition (42 ± 19 mL/min [0.70 ± 0.32 mL/s] versus 50 ± 22 mL/min [0.83 ± 0.37 mL/s]; $P = 0.004$). Prevalences of insomnia in groups according to eGFR were 5% (12 of 236 patients), 7% (36 of 505 patients), and 14% (19 of 138 patients) for the groups with GFRs greater than 60 mL/min (>1.00 mL/s), 30 to 60 mL/min (0.50 to 1.00 mL/s), and less than 30 mL/min (<0.50 mL/s), respectively ($P < 0.01$). Patients with insomnia had significantly lower serum albumin and mean hemoglobin levels than patients without the condition (Table 2).

Transplant vintage and immunosuppressive medications. Transplant vintage was not associated with insomnia: median time since transplantation was similar in patients with and without the condition (Table 2). None of the individual immunosuppressive medications or mutually exclusive combinations of immunosuppressives was associated significantly with insomnia (not shown).

Presence of RLS, obstructive sleep apnea syndrome, or other comorbid conditions. The presence of several sleep disorders was associated with insomnia in different populations studied to date. The prevalence of RLS and obstructive sleep apnea in the chronic kidney disease population is suggested to be much greater than in the general population. In our transplant population, the presence of RLS and high risk for obstructive sleep apnea were associated with significantly higher AIS scores than the absence of these conditions (median, 6 [IQR, 6] versus median, 2 [IQR, 4] and median, 4 [IQR, 5] versus median, 2 [IQR, 3] for RLS and obstructive sleep apnea, respectively; $P < 0.001$ for both). Furthermore, the prevalence of these conditions was significantly greater in patients with than without insomnia (Table 2).

Insomnia is associated with increased comorbidity in diverse patient populations. In our transplant recipients, the number of self-reported comorbid conditions was significantly higher in the insomniac group than in patients without insomnia (Table 2).

Multivariate analysis. To assess the independent association between severity of insomnia symptoms and variables that showed significant or marginal association with insomnia in bivariate analysis, a negative binomial regression model was built with AIS score as the dependent variable. Negative binomial regression was used because the distribution of AIS scores deviated substantially from normal distribution. The following independent variables were entered in the model: age, sex, serum hemoglobin level, eGFR, presence of RLS, high risk for obstructive sleep apnea, number of self-reported comorbid conditions, and CES-D score. In this model, CES-D score, high risk for obstructive sleep apnea, number of self-reported comorbid conditions, and presence of RLS, but not age, sex, or renal function, were associated significantly and independently with AIS score (Table 3). Qualitatively similar associations were seen when the presence of insomnia was assessed in a logistic regression model with the same independent variables in the model (not shown).

Hypnotic use. Of 884 transplant recipients, 54 patients (6%) reported regular (at least 1 to 2

Table 3. Negative Binomial Logistic Regression Model for AIS Score in the Transplant Population

	Odds Ratio	95% Confidence Interval for Odds Ratio		Chi-Square	*P*
		Lower	Upper		
Age	1.001	0.996	1.006	0.12	0.724
Sex	1.071	0.994	1.219	1.06	0.302
Serum hemoglobin	0.999	0.996	1.003	0.00	0.945
Calculated GFR	0.999	0.996	1.002	0.70	0.403
No. of self-reported comorbid conditions	1.068	1.030	1.108	12.49	<0.001
Presence of RLS	1.397	1.067	1.829	5.9	0.015
High risk for obstructive sleep apnea syndrome	1.337	1.169	1.530	17.96	<0.001
CES-D score (depression)	1.044	1.037	1.040	171.87	<0.001

times/wk) use of sleeping pills. The prevalence of hypnotic agent use was similar in the transplant and wait-listed groups (transplant, 6% versus wait-listed, 7%; P = not significant). Transplant recipients who used sleep medications were older (53 ± 10 versus 48 ± 12 years; $P = 0.005$) and the proportion of women was greater (59% versus 41%; $P = 0.007$) in the group of sleeping pill users. Furthermore, patients who used hypnotics regularly were more likely to have insomnia (33% versus 6%; $P < 0.001$) and be depressed (48% versus 25%; $P < 0.001$) than patients who did not report regular hypnotic use.

Insomnia in Transplant Recipients Versus Dialysis Patients

Both AIS score and prevalence of insomnia was significantly lower in the transplant versus wait-listed groups ($P < 0.001$ for both comparisons; Table 1). To assess whether living with a functioning kidney graft was associated independently with better sleep or lower prevalence of insomnia, a series of multivariate analyses were carried out.

First, a negative binomial logistic regression model was built with AIS score as the outcome variable. All variables that were independently associated with AIS score in the transplant group, namely, self-reported comorbidity, presence of RLS, high risk for obstructive sleep apnea syndrome, and CES-D score, were entered as explanatory variables, in addition to treatment modality (transplantation versus wait listing). In this model, living with a functioning kidney graft was associated significantly with lower AIS score, which means better sleep, even after adjusting for the other variables (Table 4).

In a logistic regression analysis with the presence or absence of insomnia as the dependent variable and the same independent variables as in the described model, treatment modality was not a significant predictor of insomnia (Table 5, right side). Because of the robust and complex bidirectional cause and consequence association between insomnia and depression, the analysis was repeated after removing depression score

Table 4. Negative Binomial Logistic Regression Model for AIS Score in the Transplant and Wait-Listed Populations

	Odds Ratio	95% Confidence Interval for Odds Ratio		Chi-Square	*P*
		Lower	Upper		
Modality (wait listing *v* transplantation)	1.333	1.164	1.527	17.20	<0.001
No. of self-reported comorbid conditions	1.054	1.021	1.088	10.34	0.001
Presence of RLS	1.491	1.206	1.844	13.63	<0.001
High risk for obstructive sleep apnea syndrome	1.283	1.141	1.443	17.31	<0.001
CES-D score (depression)	1.042	1.036	1.048	201.88	<0.001

Table 5. Binary Logistic Regression Model of the Presence or Absence of Insomnia in the Transplant and Wait-Listed Populations

	Without CES-D Score Entered				With CES-D Score in the Model			
	Odds Ratio	95% Confidence Interval for Odds Ratio		*P*	Odds Ratio	95% Confidence Interval for Odds Ratio		*P*
Modality (transplantation *v* wait listing)	1.871	1.072	3.266	0.028	1.708	0.936	3.266	0.081
No. of self-reported comorbid conditions	0.834	0.728	0.956	0.009	0.926	0.799	1.074	0.310
Presence of RLS	5.683	2.922	11.052	<0.001	4.071	1.984	8.354	<0.001
High risk for obstructive sleep apnea syndrome	2.486	1.522	4.063	<0.001	1.769	1.040	3.009	0.035
CES-D score (depression)	NA	NA	NA	NA	0.913	0.891	0.935	<0.001

Abbreviation: NA, not applicable.

from the model. In this second analysis, treatment modality (transplantation versus wait listing) was associated significantly with the presence of insomnia after adjusting for the presence of RLS, high risk for obstructive sleep apnea, and number of self-reported comorbid conditions (Table 5, left side).

DISCUSSION

In this report, we show for the first time that the prevalence of insomnia, assessed by using the AIS, is significantly less in kidney transplant recipients than wait-listed dialysis patients with similar sociodemographic characteristics. Transplant recipients also had a lower prevalence of individual insomnia symptoms and lower AIS scores than wait-listed patients. Living with a transplanted kidney remained a significant independent predictor of lower AIS score (ie, better sleep), even after statistical adjustment for important covariates in a multivariate analysis (Table 4). The prevalence of insomnia also remained significantly less in the transplant group after controlling for differences in comorbidity and presence of primary sleep disorders (RLS and obstructive sleep apnea; Table 5). The difference in prevalence of insomnia between transplant recipients versus wait-listed patients failed to reach statistical significance after entering CES-D score into the logistic regression (Table 5). These results clearly point to the importance of depression as a strong and potentially modifiable risk factor for insomnia in patients with chronic kidney disease (discussed later). However, these results also suggest that living with a functioning kidney graft (as opposed to receiving maintenance dialysis) is associated with better overall sleep quality. The underlying mechanisms are unknown, but the more physiological metabolic status or less intrusive treatment of transplant recipients may contribute to these observed differences.

The observed prevalence of insomnia in the wait-listed group was substantially less than what was suggested earlier for nonselected dialysis patients.[1,5,6] This difference is explained in part because earlier reports, including our earlier work, relied on the presence of insomnia symptoms instead of using diagnostic criteria for insomnia. Furthermore, wait-listed patients are likely to be younger and healthier than the rest of the dialysis population, and this important difference makes it difficult to compare our results with previous data. Our preliminary results obtained by using the AIS in approximately 1,000 nonselected dialysis patients suggest an insomnia prevalence of approximately 20% in that population (M. Novak, Sz. Barotfi, A. Bana et al, unpublished observation, December 2003).

We also had the unique opportunity to compare these results with data obtained in a large nationally representative sample. In this comparison, the prevalence of insomnia in the transplant group was similar to that in the general population. At the same time, mean AIS score and prevalence of some of the insomnia symptoms were significantly higher in the transplant group than the general population group.

The finding that transplant recipients have a prevalence of insomnia similar to the general

population is surprising. Although it was documented that renal transplantation improves clinical outcomes, including quality of life, transplant recipients have multiple comorbidities and use several medications that may potentially interfere with sleep. Furthermore, Sabbatini et al,[23] using the Pittsburgh Sleep Quality Index, recently reported a 52% prevalence of "poor sleep" in a sample of kidney transplant recipients compared with the 8% prevalence of insomnia in our transplant group. This substantial difference can be explained in part by differences in study populations and, perhaps more importantly, different instruments used to assess sleep. The prevalence of individual insomnia symptoms in our data set was similar to numbers reported by Sabbatini et al[23] (Fig 1). The Pittsburgh Sleep Quality Index assesses a wide variety of factors associated with sleep. Conversely, the AIS focuses on features required for the diagnosis of chronic insomnia. The cutoff score of 10, suggested in the validation work of Soldatos et al,[18] establishes stringent diagnostic criteria. However, we believe these criteria are justified because this approach in our recent survey in a nationally representative sample[13] yielded results similar to those reported from epidemiological surveys in other European countries.[8]

Although the prevalence of patients fulfilling diagnostic criteria for insomnia was similar in the transplant and general-population groups, AIS score, representing "overall sleep quality," was significantly higher in the transplant group, similar to findings of Sabbatini et al.[23] Furthermore, the prevalence of patients reporting at least 1 chronic insomnia symptom also was greater in the transplant group than in the general-population sample. Our yet unpublished results suggest that the presence of even 1 mild insomnia symptom is associated with significantly impaired daytime functioning (M. Novak, J. Rethelyi, M. S. Kopp, I. Mucsi, unpublished results, January 2004). We propose that these patients' lives currently may not be affected severely by insomnia; however, they may be at increased risk for subsequently developing chronic insomnia if the underlying condition leading to the sleep problems persists. We suggest that prospective studies focusing on this population to assess the natural course of insomnia symptoms are warranted.

We also analyzed sociodemographic and clinical correlates of insomnia in transplant recipients. Our results are different than what was reported previously for the general population. In our data set, insomnia was not associated with age or sex in multivariate analysis. We do not have clear explanations for these findings; however, similar results were reported for dialysis patients in several studies, including our earlier report.[6] It is possible that modifier factors related to renal failure, comorbid conditions, or medications may alter the distribution of insomnia compared with the general population.

Depression, measured by using the CES-D Scale, was the most powerful independent predictor of AIS score and the presence of insomnia in both the transplant group and the whole chronic kidney disease population in multivariate models. Similar findings were published for both the general population[34,35] and patients with chronic diseases.[36,37] There is a complex and bidirectional association between depression and insomnia and a potential overlap between these 2 entities, especially when self-reported instruments are used to detect the conditions. Insomnia is 1 of the main symptoms of psychological distress; however, it also may be a precursor to depression. However, the cross-sectional design of our study precludes a conclusion on directionality or causality. At the same time, we think it is very important to recognize this association because it is essential for clinicians to target both psychological and medical risk factors associated with insomnia, especially those that potentially are modifiable, such as depression.

Insomnia was associated with declining renal function in kidney transplant recipients in bivariate analysis. However, renal function was not associated with insomnia after statistical adjustment for covariates in multivariate analysis. This may suggest that increased depression or comorbidity (including RLS and/or obstructive sleep apnea) may be responsible for the observed association between declining renal function and insomnia.

Somatic or psychiatric comorbidity was associated with insomnia in different populations,[8,36] as in the present study. The number of self-reported comorbid conditions was independently and significantly associated with AIS score in the transplant group. Furthermore, it remained an

independent predictor of AIS score in the total chronic kidney disease population, even after statistical adjustment for the presence of sleep disorders, depression, and treatment modality (transplantation versus wait listing). Unfortunately, we cannot tell from our analysis which aspects of the comorbid conditions (eg, pain, disease symptoms, or medications) impact on sleep.

Insomnia frequently is associated with specific sleep disorders, such as obstructive sleep apnea syndrome or RLS.[5,25,38] In this study, both RLS and obstructive sleep apnea syndrome were independent and significant predictors of insomnia after controlling for covariables. With regard to RLS, we reported similar findings from a different study involving a large number of dialysis patients.[25] Because both RLS and obstructive sleep apnea syndrome are potentially treatable conditions, it is conceivable that treatment of those sleep disorders also would alleviate associated insomnia.

Approximately 6% of the patients enrolled in this study reported regular use of hypnotics. Female sex and the presence of chronic insomnia were associated independently with hypnotic use. These findings are in agreement with results of an earlier survey recruiting a representative population-based sample.[39] Long-term use of sleeping pills lacks demonstrable benefit and clearly is of concern in the transplant population, as well.

Our study is notable for the large number of enrolled patients and also the extensive clinical and sociodemographic data collected in the survey. Furthermore, basic characteristics of the transplant and wait-listed groups are similar, making direct comparison between these 2 groups reliable. We believe the use of a matched sample derived from a nationally representative sample adds additional value to our analysis. Finally, the instrument we used to identify patients with insomnia is a standard validated questionnaire, which makes our results comparable to other studies using standard methods.

Conversely, we acknowledge the limitation imposed by the cross-sectional design of our survey, making directional or causal conclusions impossible. Also, this is a single-center study; therefore, results may not be readily generalizable. Finally, because we did not have complete data for all medical diagnoses of patients, we used a self-reported comorbidity score.[24,25] In a cross-sectional analysis, self-reported comorbidity correlated significantly with several domains of the 36-Item Short-Form Health Survey instrument in both dialysis and kidney transplant patients. It also correlated weakly, but significantly, with serum albumin level.[40] Therefore, we suggest that this score provides valuable information and it correlates with the overall clinical condition of patients.

In summary, we found a substantially lower prevalence of insomnia in kidney transplant recipients than wait-listed dialysis patients. The prevalence observed in the transplant group is similar to that observed in the general population. Importantly, we identified a substantial proportion of transplant recipients who did not fulfill the diagnostic criteria of insomnia, but reported at least 1 insomnia symptom that potentially could be associated with impaired daytime functioning. Finally, insomnia in this population is associated with increased level of depression and the presence of RLS and obstructive sleep apnea syndrome. These conditions potentially are treatable; therefore, attention should be directed to their appropriate diagnosis and management because successful treatment of factors related to insomnia or attending insomnia itself may improve clinically important outcomes, such as quality of life, in kidney transplant recipients.

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